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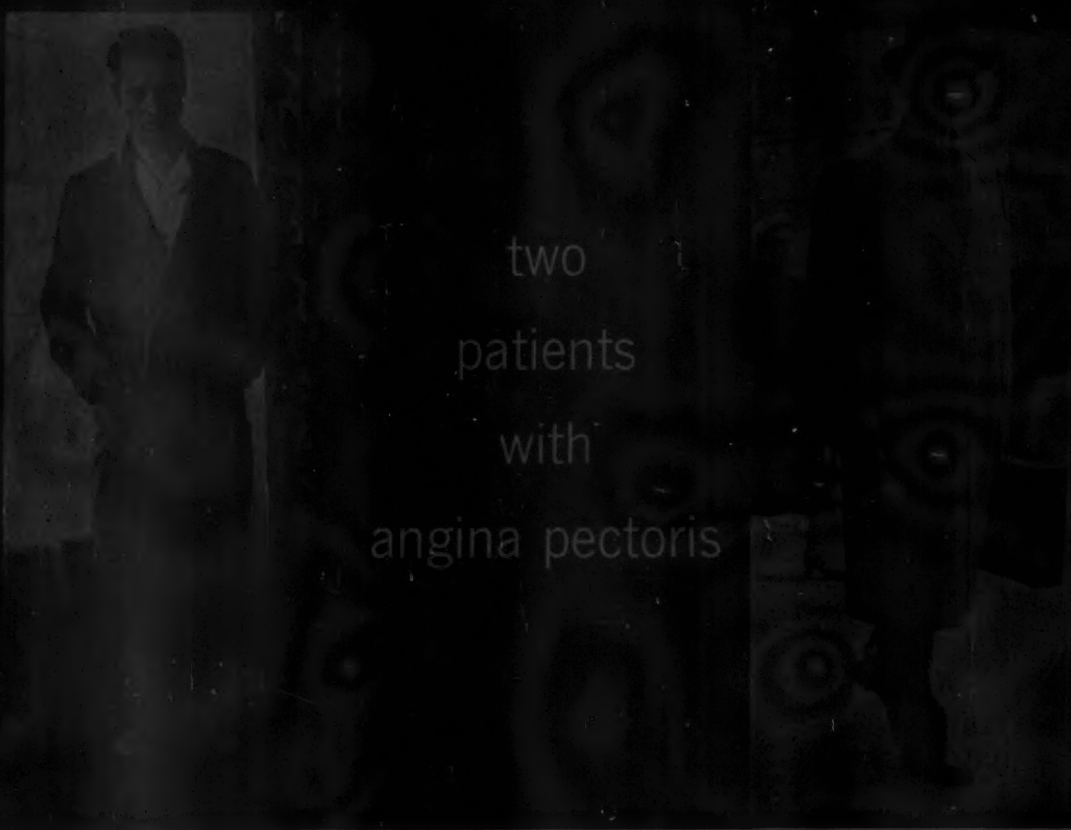

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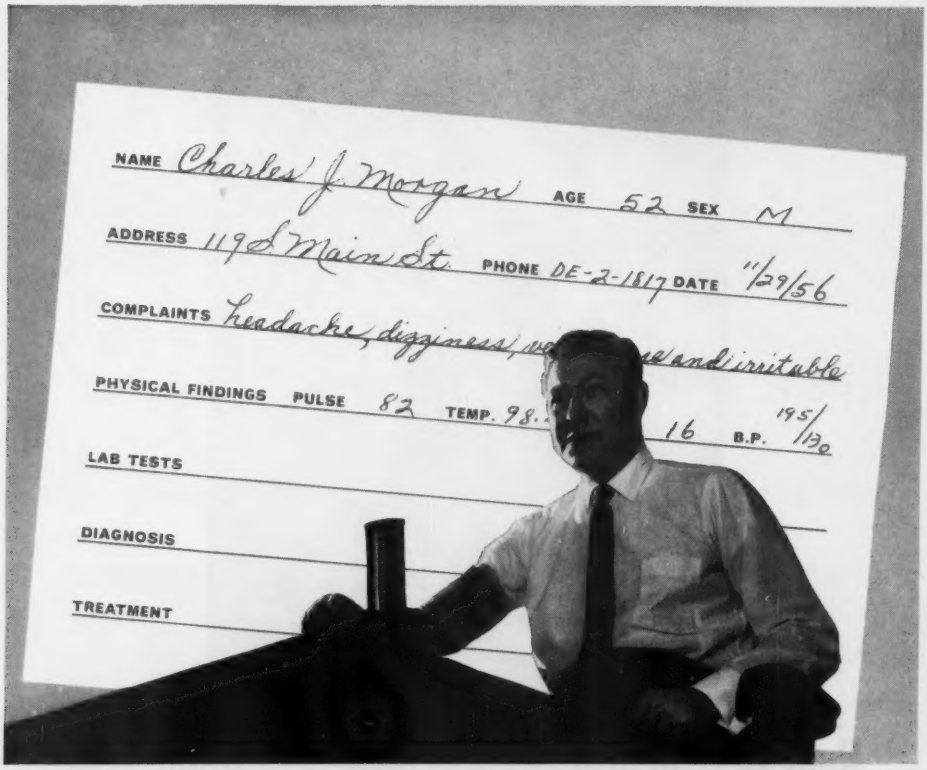
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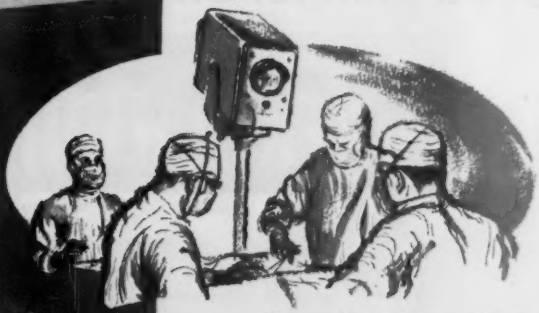

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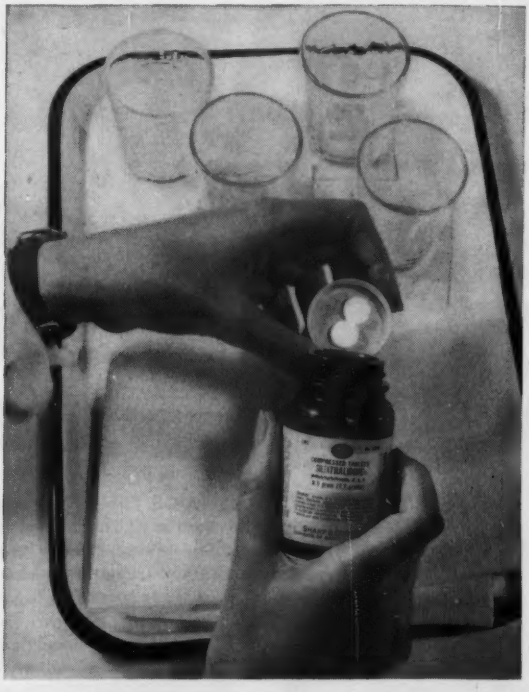

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AMPULS for your bag. For immediate control of drug-, disease- or irradiation-induced vomiting. Dramatic results often obtained in cases unrelieved by other antiemetics. 25 mg. (1 cc.) and 50 mg. (2 cc.) ampuls in boxes of 6.

SUPPOSITORIES. When oral doses cannot be retained and when injections are not practicable—these are the obvious answer. Rapidly absorbed. Two strengths: 100 mg. for adults, and 25 mg. for children.

SYRUP for pediatric use. Often one dose stops the vomiting of gastroenteritis. Each 5 cc. (1 teaspoonful) contains 10 mg.

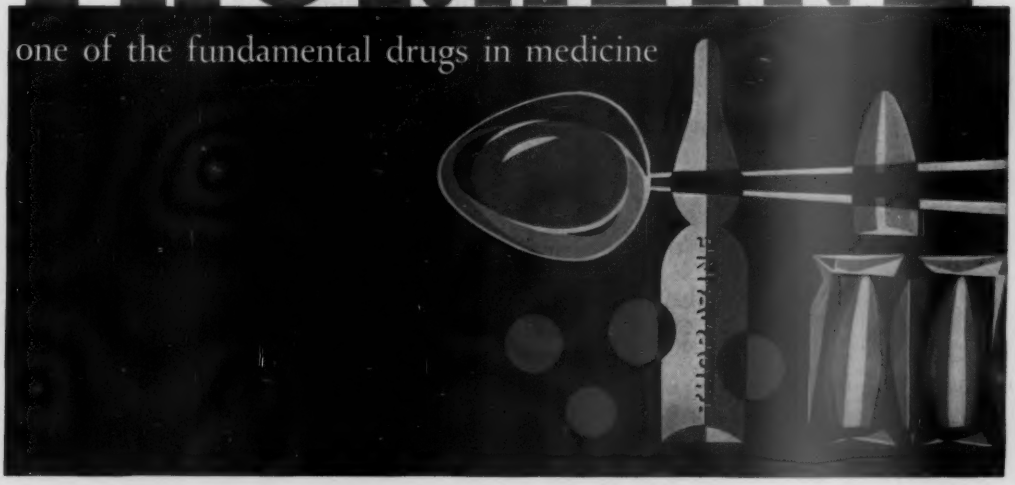
TABLETS when oral dosage is feasible. Available in 10, 25, 50 and 100 mg. tablets.

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

THORAZINE*

one of the fundamental drugs in medicine



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Every woman who suffers in the menopause deserves "Premarin," widely used natural, oral estrogen.

"Premarin" produces prompt symptomatic relief and a gratifying "sense of well-being." "Premarin" presents the complete equine estrogen-complex. Has no odor, imparts no odor.

"PREMARIN"®
Conjugated estrogens (equine)

in the menopause and the pre- and postmenopausal syndrome

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relieves cough—

...specifically,
by direct suppression
of the cough reflex.
But unlike narcotics,
Romilar does not cause
central depression,
drowsiness, constipation,
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Available as syrup,
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(c NH_4Cl).

Romilar® HBr – brand of dextromethorphan HBr

in a single tablet —

pain relief
plus
antibacterial action

AZO GANTRISIN

In urinary tract infections, Azo Gantrisin usually provides effective antibacterial control (local and systemic), together with prompt relief of associated pain and discomfort . . . by combining well-tolerated Gantrisin with a clinically proved urinary analgesic.

ROCHE

Each Azo Gantrisin tablet contains 0.5 Gm Gantrisin 'Roche' plus 50 mg phenylazo-diamino-pyridine HCl.

Gantrisin® - brand of sulfisoxazole

increasingly preferred

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strikingly effective

for patients

in rheumatoid arthritis

METICORTEN*

(PREDNISONE)

excellent relief of pain, swelling, tenderness; diminishes joint stiffness—facilitates early physical therapy—expedites rehabilitation

dietary regulations usually unnecessary

minimizes incidence of electrolyte imbalance

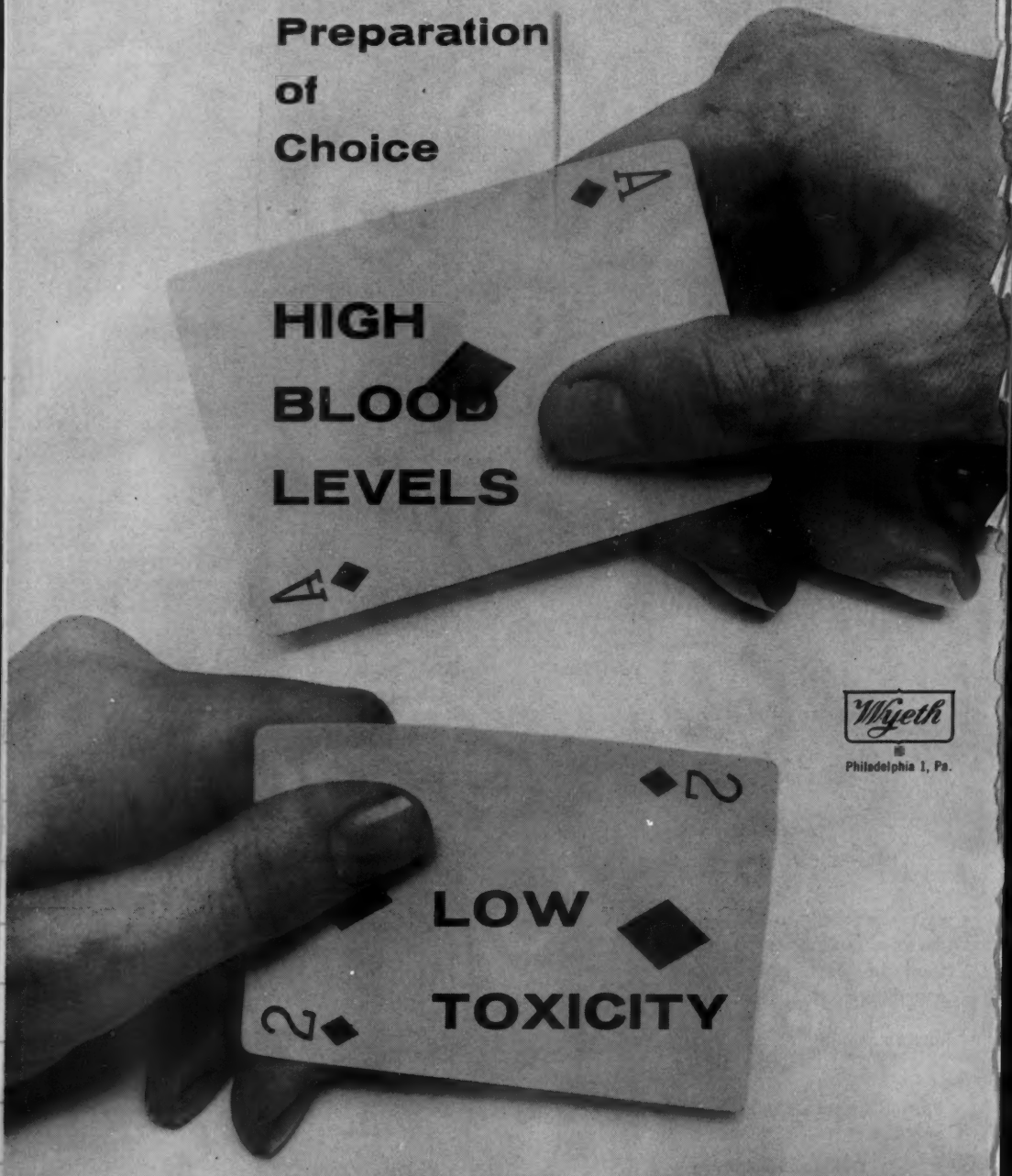
1, 2.5 and 5 mg. tablets

METICORTEN,* brand of prednisone.

*T. M. MC-J-2378

In Urinary-Tract Infections

Preparation of Choice



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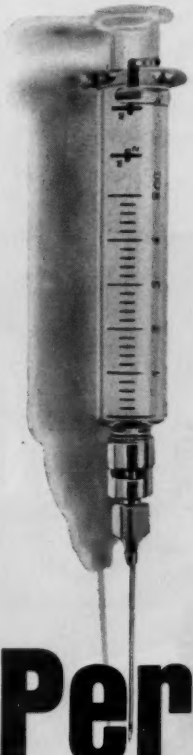
Triple Sulfonamides
(Sulfadiazine, Sulfamerazine, Sulfamethazine)

only one injection a month



Percorten®

trimethylacetate

(desoxycorticosterone trimethylacetate CIBA)

controls adrenocortical insufficiency

One monthly injection of Percorten affords prolonged, well-regulated hormone therapy for patients with Addison's and other diseases marked by adrenocortical insufficiency...

- **without** annoying and painful daily injections
- **without** unpleasant implantation of pellets

Multiple-dose Vials, 4 ml., each ml. containing 25 mg. Percorten trimethylacetate as an aqueous microcrystalline suspension for intramuscular use only.

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SUMMIT, N. J.

added certainty in antibiotic therapy

–particularly for that 90% of the patient population treated in home or office where sensitivity testing may not be practical . . .

for your entire patient population

Sigmam

multi-spectrum†

100% EFFECTIVE in respiratory infections including the 25% due to resistant staphylococci.[1-3]

97% EFFECTIVE in dermatologic and mixed soft tissue infections including the 22% resistant to one or more antibiotics.[3-6]

84.6% EFFECTIVE in genitourinary infections including the 61% resistant to other antibiotic therapy.[2,5]

93% EFFECTIVE in diverse infections including the 21% due to resistant pathogens.[1,5]

98.7% EFFECTIVE in tropical infections including those complicated by heavy bacterial contamination or multiple parasitisms.[7]

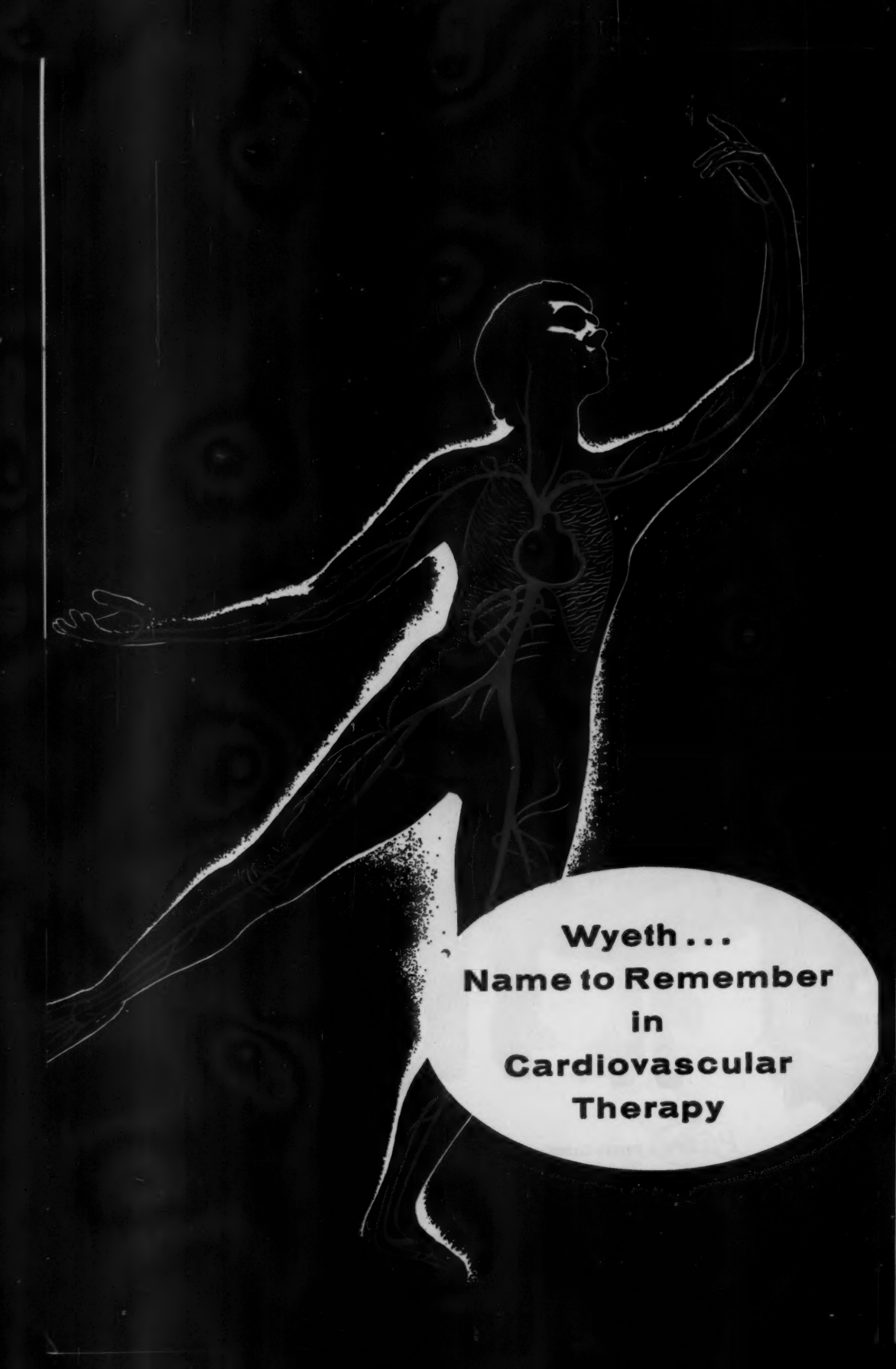
†the antimicrobial spectrum of tetracycline extended and potentiated with oleandomycin (Matromycin®) to combat resistant strains of pathogens—particularly resistant staphylococci—and to delay or prevent the emergence of new antibiotic-resistant strains.

1. Carter, C. H., and Maley, M. C.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 51. 2. Shalowitz, M., and Sarnoff, H. S.: Personal communication. 3. Shubin, M.: Personal communication. 4. La Caille, R. A., and Prigot, A.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 67. 5. Winton, S. S., and Chesterow, E.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 55. 6. Cornbleet, T.: Personal communication. 7. Loughlin, E. H.; Mullin, W. G.; Alcinder, L., and Joseph, A. A.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 63.

SUPPLY
CAPSULES: 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.). Bottles of 16 and 100.
new mint-flavored ORAL SUSPENSION: 1.5 Gm., 125 mg. per 5 cc. teaspoonful (oleandomycin 42 mg., tetracycline 83 mg.) 2 oz. bottle.

Pfizer

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y.
World leader in antibiotic development and production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Name to Remember
in
Cardiovascular
Therapy

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TARTRATE (Pentolinium Tartrate)

Indicated in moderately severe, severe, and uncomplicated malignant hypertension. The action of ANSOLYSEN is potent, reliable, and prolonged. It lowers blood pressure, relieves symptoms, offers minimal by-effects.

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Indicated in congestive heart failure. PURODIGIN achieves and maintains digitalization with the smallest oral dose of all cardioactive glycosides. It offers high potency, complete absorption, steady maintenance, uniform action.

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Indicated for diuretic therapy. THIOMERIN produces significantly effective, smooth, and persistent fluid loss. It is well tolerated when given subcutaneously and, of all organomercurial diuretics, is least irritant.

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SULFATE INJECTION

(Mephentermine Sulfate)

Indicated in acute hypotensive states not associated with hemorrhage. Injection WYAMINE is an effective and predictable pressor agent. It may be used intravenously or intramuscularly for either prophylaxis or therapy of hypotension.

"Well, then, how about *en brochette?*"

And—while we're stretching a point – what about all those folks who choose one kind of dish, stick with it, eat it all day, every day . . . only to discover (to their chagrin) that they've shortchanged themselves nutritionally? Especially in the important B-complex vitamins. So, for deficiences brought about by unsound mealtime habits or because of illness, senility, stress, or postoperative states, remember SUR-BEX with C. As a dietary supplement: 1 or 2 tablets daily. For postoperative convalescence: 2 or more daily.

Abbott

Just one SUR-BEX tablet a day supplies:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} (as cobalamin concentrate)	2 mcg.
Calcium Pantothenate	10 mg.
Ascorbic Acid	150 mg.
Desiccated Liver, N.F.	300 mg.
Brewer's Yeast, Dried	150 mg.

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ABBOTT'S B-COMPLEX TABLETS WITH C

703100

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Overcoming Today's No. 1 Nutritional Problem

Knox "Food Exchange" Diet Enlists the Cooperation of Your DIABETIC Patients for Dietotherapy

1. This Knox booklet is based on nutritionally-tested Food Exchanges[1] and demonstrates that variety is possible for diabetic diets.

2. The easy-to-understand Food Exchanges simplify dietary control for the diabetic by eliminating calorie counting.

3. Diets promote accurate adjustment of caloric levels to the special needs of the patient, yet allow each individual considerable latitude in the choice of foods.

4. Each booklet presents in addition 16 pages of appetizing, kitchen-tested recipes.

1. The Food Exchange Lists referred to are based on material in "Meal Planning with Exchange Lists" prepared by Committees of the American Diabetes Association, Inc., and The American Dietetic Association in cooperation with the Chronic Disease Program, Public Health Service, Department of Health, Education and Welfare.

Chas. B. Knox Gelatine Co., Inc.
Professional Service Dept. AI-2
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Please send me ..... dozen copies of the Knox diabetic brochure describing the use of Food Exchange Lists.

Your Name and Address

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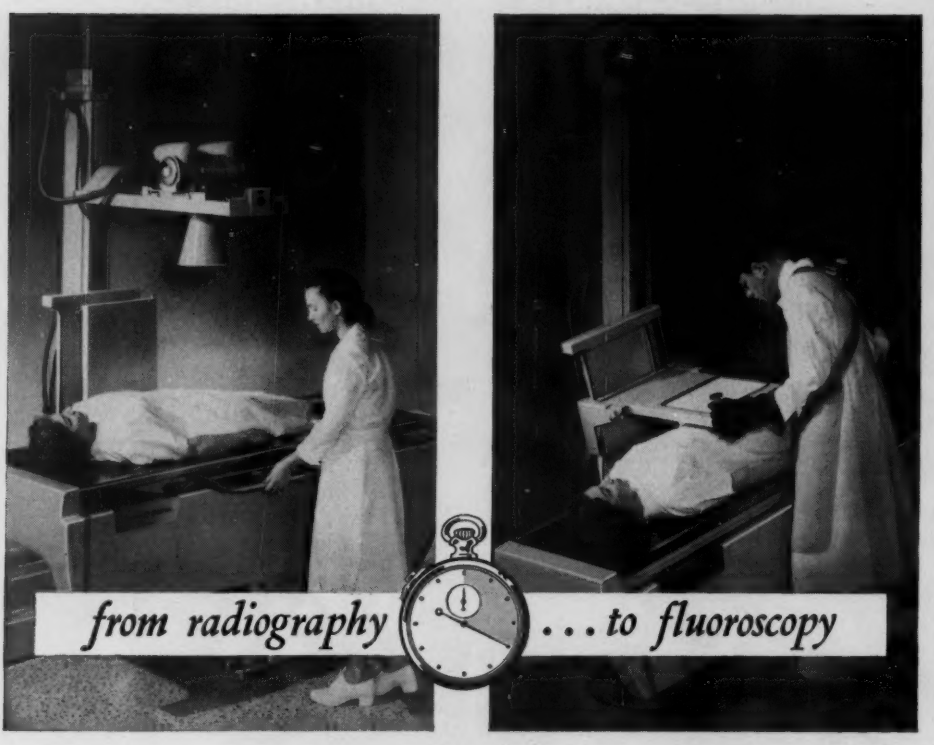

. . . in a matter of seconds

— and those seconds are *split* in radiography with Patrician's stop-motion 200-ma, 100-kvp, full-wave power. Involuntary movements of patients or organs no longer need be your problem — nor the heavy investment formerly required for x-ray equipment capable of overcoming them.

At a price competitive with low-power, limited-range apparatus, you can now enjoy *full* x-ray facilities offered by the General Electric Patrician: kenotron-rectified output for longer x-ray tube life . . . 81-inch angulating table for those tall patients . . . double-focus rotating-anode tube for radiography *and* fluoroscopy . . . highly maneuverable independent tube stand . . . fully counterbalanced fluoroscopic screen . . . compact, simplified control unit.

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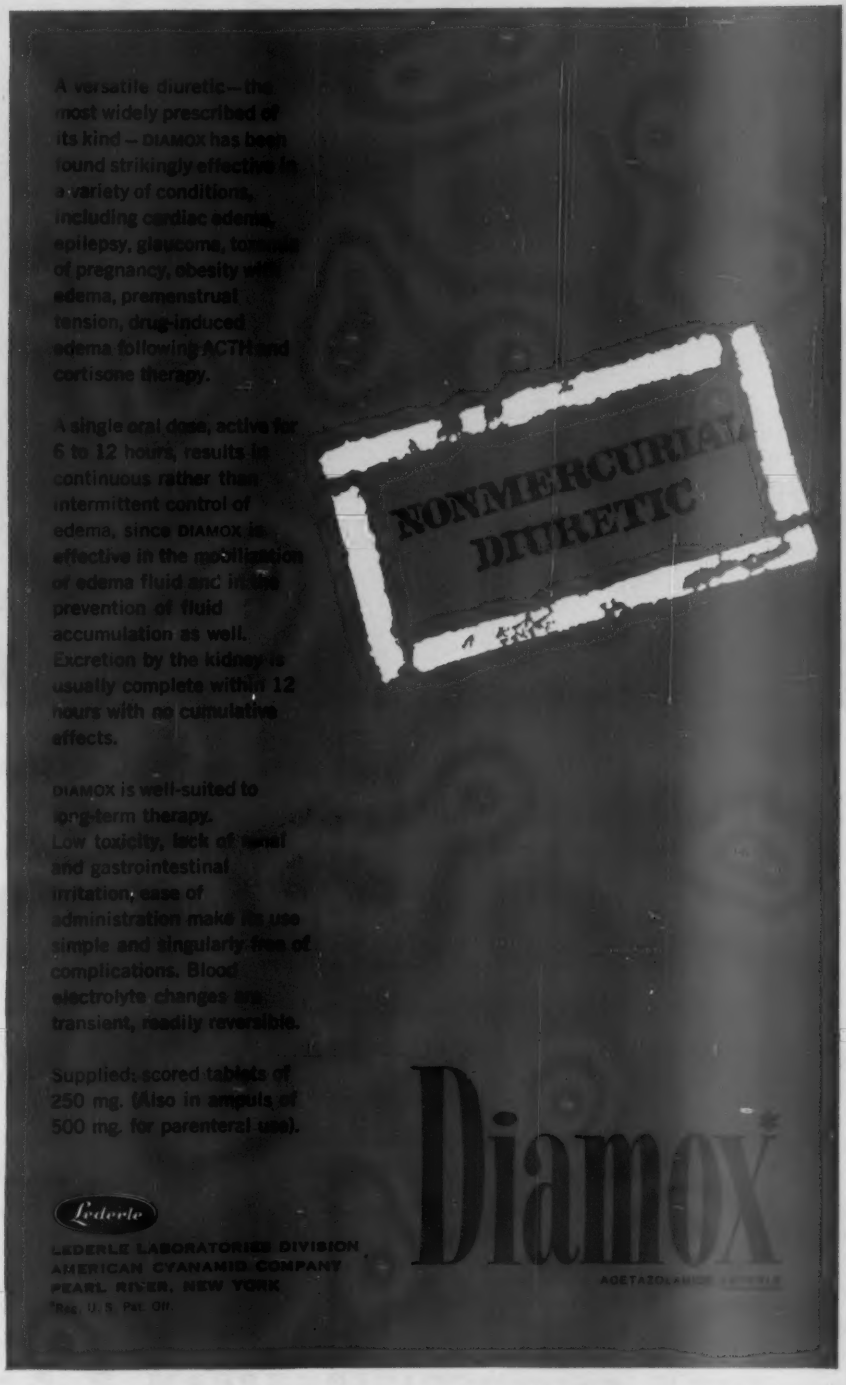
A versatile diuretic—the most widely prescribed of its kind—DIAMOX has been found strikingly effective in a variety of conditions, including cardiac edema, epilepsy, glaucoma, toxemia of pregnancy, obesity with edema, premenstrual tension, drug-induced edema following ACTH and cortisone therapy.
A single oral dose, active for 6 to 12 hours, results in continuous rather than intermittent control of edema, since DIAMOX is effective in the mobilization of edema fluid and in the prevention of fluid accumulation as well. Excretion by the kidney is usually complete within 12 hours with no cumulative effects.
DIAMOX is well-suited to long-term therapy. Low toxicity, lack of renal and gastrointestinal irritation, ease of administration make its use simple and singularly free of complications. Blood electrolyte changes are transient, readily reversible.
Supplied: scored tablets of 250 mg. (Also in ampuls of 500 mg. for parenteral use).
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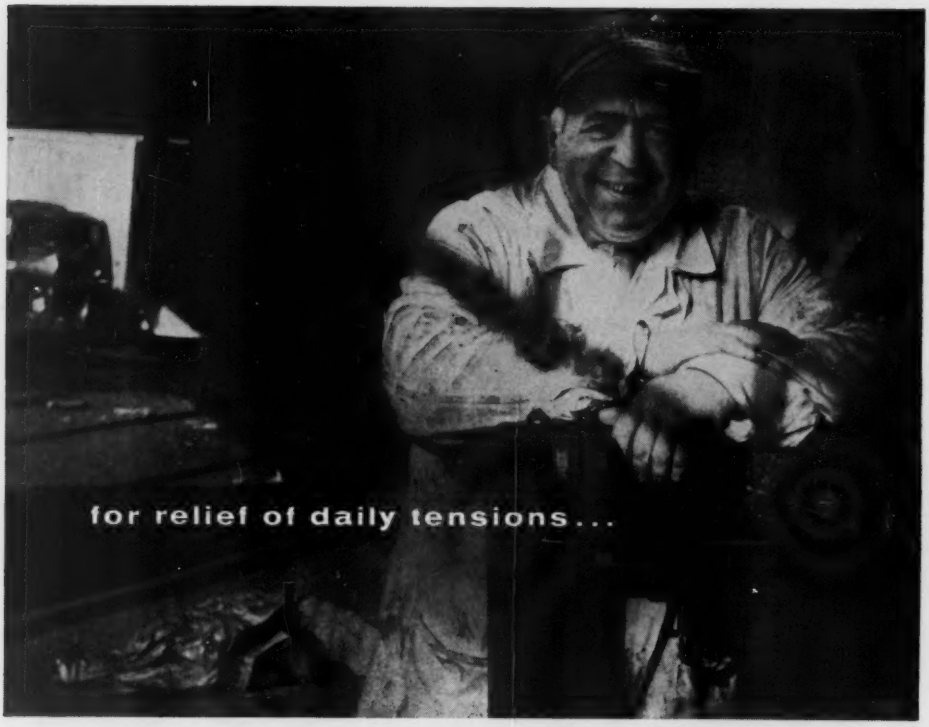

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Ectylurea, AMES
(higher melting isomer of
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the power of gentleness

helps patients face everyday anxieties and tensions

*"...mild action promotes an over-all calmness..."**

New and Different • not a hypnotic-sedative—unrelated to any available chemo-psychotherapeutic agent • no evidence of cumulation or habituation • does not cause gastric hyperacidity • unusually wide margin of safety—no significant side effects

Dosage: 150-300 mg. three or four times daily.

Supplied: 300 mg. scored tablets, bottles of 48.

*Ferguson, J. T.: J. Am. Geriatrics Soc. *4*:1080, 1956.

AMES COMPANY, INC • ELKHART, INDIANA 24956

In the arthritides . . . a prudent course

Ulysses and the Sirens—from a vase in the British Museum

between the hazards of high steroid dosage
and the frustration of inadequate relief

Because of the complementary action of cortisone and the salicylates, Salcort produces a greater therapeutic response with lower dosage.

One study concludes: "Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."[1]

SALCORT®*

indications:

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Neuromuscular affections.

[1]Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. *11*:1105.

each tablet contains:

Cortisone acetate	2.5 mg.
Sodium salicylate	0.3 Gm.
Aluminum hydroxide gel, dried	0.12 Gm.
Calcium ascorbate (equivalent to 50 mg. ascorbic acid)	60.0 mg.
Calcium carbonate	60.0 mg.

**U.S. Pat. 2,691,662*

The S. E. MASSENGILL Company, Bristol, Tennessee

NEW YORK • KANSAS CITY • SAN FRANCISCO

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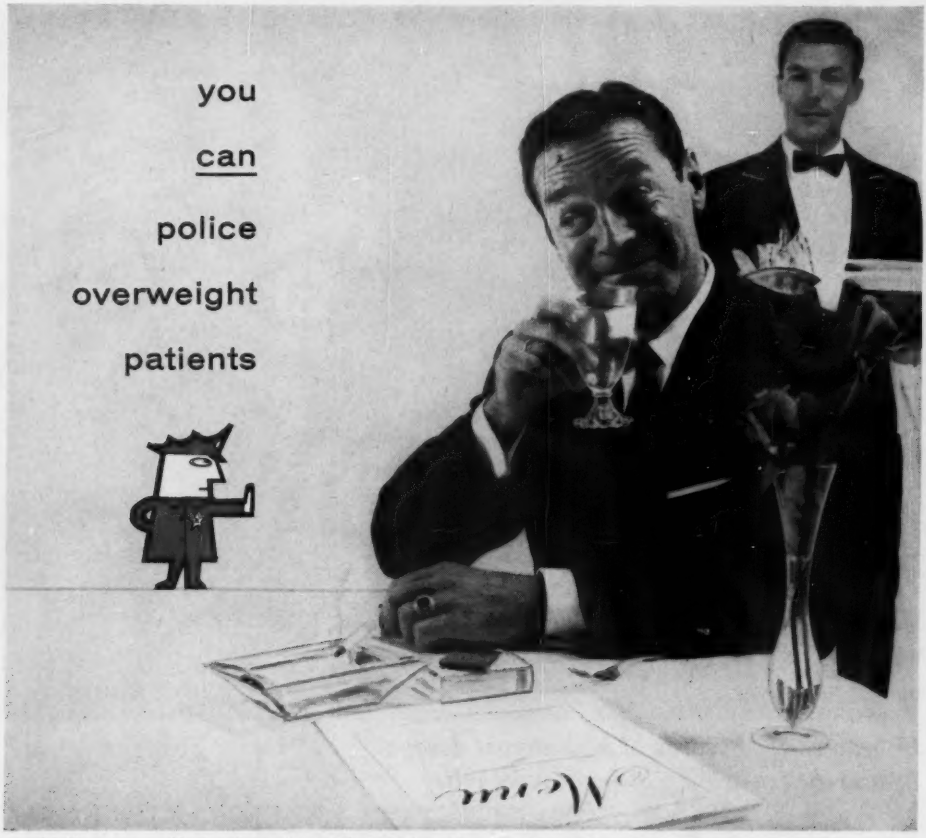

When a diet sheet with didactic instructions is not enough . . .

assign REVICAPS to police the appetite of your overweight patients.

REVICAPS safely curb the frustrations and hunger contractions that break dietary discipline during the initial difficult phase of weight reduction.

REVICAPS combine all three accepted adjuncts to healthy weight reduction: d-amphetamine, methylcellulose, vitamins and minerals.

Include REVICAPS in the reducing regimen you prescribe.

Available on Prescription Only

dry filled sealed capsules

REVICAPS* accepted reducing medication

d-Amphetamine-Methylcellulose-Vitamins and Minerals

Dosage: 1 or 2 capsules ½ to 1 hour before meals.

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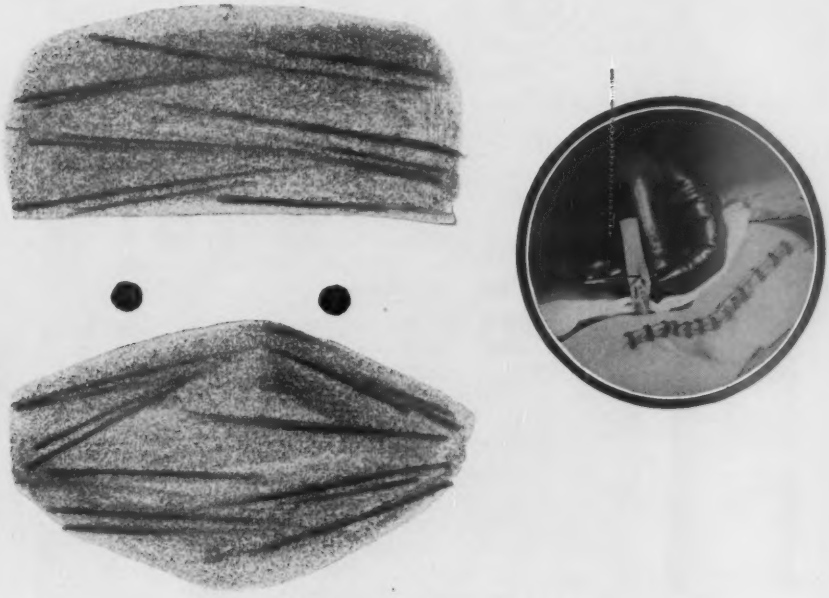

"three eyes are better than two"

Members attending the 38th Annual Session of the American College of Physicians, convening in Boston, April 8-12, will view 8 hours of "live" clinical demonstrations impossible to present before a mass audience except through the medium of color television. The "third eye" here, of course, is the lens of the camera which can be moved within inches of minute clinical subject matter. The close image captured by the camera is transmitted instantaneously to two 4½ by 6 foot color screens, where it can be seen by hundreds of viewers. When you, the reader, become a viewer, we believe you will concur with the opinion of Smith, Kline & French Laboratories that color television is an invaluable addition to the instruments of medical education.

Smith, Kline & French Laboratories, Philadelphia

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to NORMALIZE, use KONSYL®

It is important, when inducing normal bowel function, to supply a non-irritating bulk to the colon, especially in those cases in which it has been necessary to eliminate from the diet the high roughage foods containing irritating bulk (lignin and cellulose).

It has been shown[1] that the colon resumes a more normal peristaltic pattern[2] when it is supplied with a stool of medium soft consistency of sufficient bulk[3], especially if the indigestible portion of that bulk consists primarily of hemicellulose.[4]

KONSYL is a vegetable concentrate of naturally occurring hemicelluloses. It is derived from blond psyllium seed and provides just the moist, smooth, effective bulk so essential to normal peristalsis. Its use has been shown to materially hasten the rate of improvement in patients with the irritable colon syndrome.[5] KONSYL contains 100% bulk producing material.

Furthermore, Konsyl is available in 6-ounce and 12-ounce containers at significantly lower-cost-to-patient prices. That's why we say

to NORMALIZE, use KONSYL®

1. Dolkhart, R. E., Dentler, M. & Barrow, L. L., Ill. M. J. 90:286, 1946.
2. Adler, H. F., Atkinson, A. J., & Ivy, A. C., Am. J. Digest. Dis., 8:197, 1941.
3. Wozasek, D., & Steigman, F., Am. J. Digest. Dis., 9:423, 1942.
4. Williams, R. D., & Olmsted, W. H., Ann. Int. Med., 10:717, 1936.
5. Lieberthal, M. M., Conn. State M. J., 19:86, 1955.

Formula: KONSYL contains 100% platago ovata coating.

Made by BURTON, PARSONS & COMPANY *Since 1939*
Originators of Fine Hydrophilic Colloids
WASHINGTON 9, D. C.

TERGEMIST

TRADEMARK

Abbott's improved aerosol therapy for liquefying bronchial secretions

TERGEMIST assists the physician against a long-standing problem, the loosening of thick, tenacious pulmonary mucus. This new aerosol brings three mechanisms to bear on the mucus: detergent, solvent, and liquid.

Detergent

A special detergent (*sodium 2-ethylhexyl sulfate*) was chosen after comparative tests. This detergent is exceptionally prompt in its action. It requires far less volume for breaking up dried mucus, and is remarkably low in toxicity. Its "wetting" action lowers liquid surface tension, permitting moisture to penetrate and soften the thick mucus.

Solvent

The addition of *potassium iodide to* TERGEMIST provides a distinct solvent action against dried bronchial secretions. The iodide also promotes a more watery type of secretion from the bronchial glands.

Liquid

The distilled water in TERGEMIST is more than a vehicle when nebulized. It provides much-needed moisture for the softened mucus to take up. It soothes the membranes, too, and reduces the tendency toward bronchospasm.

MORE

Note these advantages in loosening thick mucus:

1. *Shorter treatment period*

   Average TERGEMIST treatment requires but *four half-hour sessions daily*. This is pleasanter for the patient, and less demanding on the attending staff.

2. *Less TERGEMIST needed*

   TERGEMIST'S superior activity requires but small volume to produce very satisfactory liquefying of the sputum. With the recommended nebulizing equipment, only three to five cc. of TERGEMIST need be nebulized per treatment period.

3. *Less apt to clog equipment*

   TERGEMIST does not contain glycerine, bicarbonate, or chemical preservatives. It consequently doesn't tend to clog nebulizing equipment. Potential sources of irritation to delicate bronchial mucosa are also thus avoided.

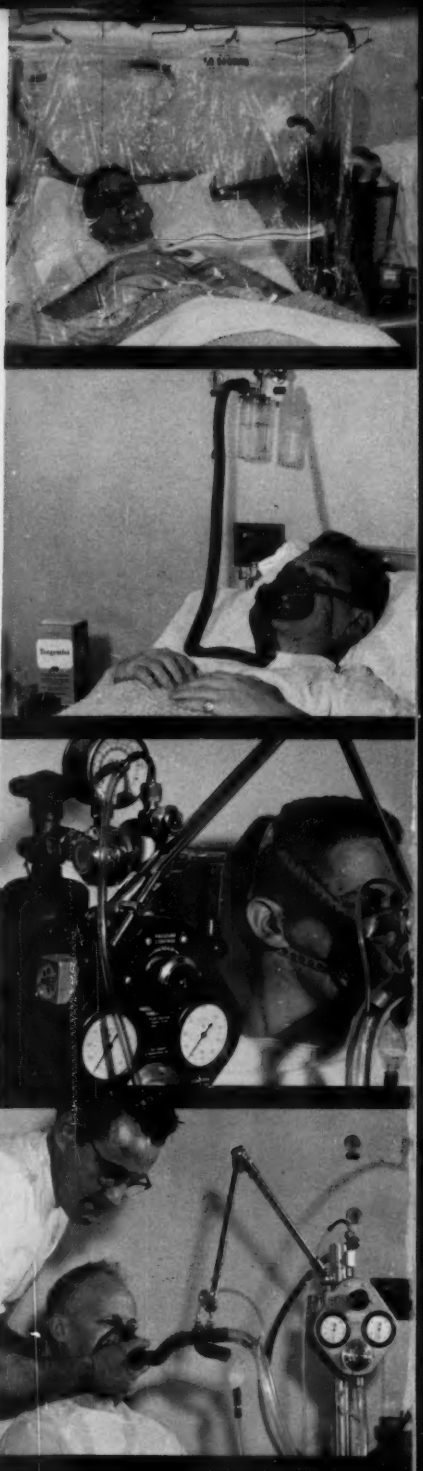
4. *Favorable clinical experience*

   TERGEMIST'S effectiveness has been proved on severe bronchopulmonary cases, ranging from childhood to old age. All patients had great difficulty in coughing up thickened mucus. Liquefaction of sputum and ease of expectoration following TERGEMIST were *good* or *excellent*[1] without exception, and many patients noted improvement after only two or three treatments. No irritation or side effects have been reported.

Abbott

TERGEMIST
TRADEMARK

Abbott's Mucolytic Aerosol Solution
Bottles of 40 cc., 250 cc., and 500 cc.
List No. 6666



TERGEMIST is administered by a nebulizer attached to a compressor or oxygen source in combination with an oral adapter, face mask, tent, etc., at the physician's discretion.

1. Levine, E. R., 1956, paper accepted for publication in *Diseases of the Chest.*

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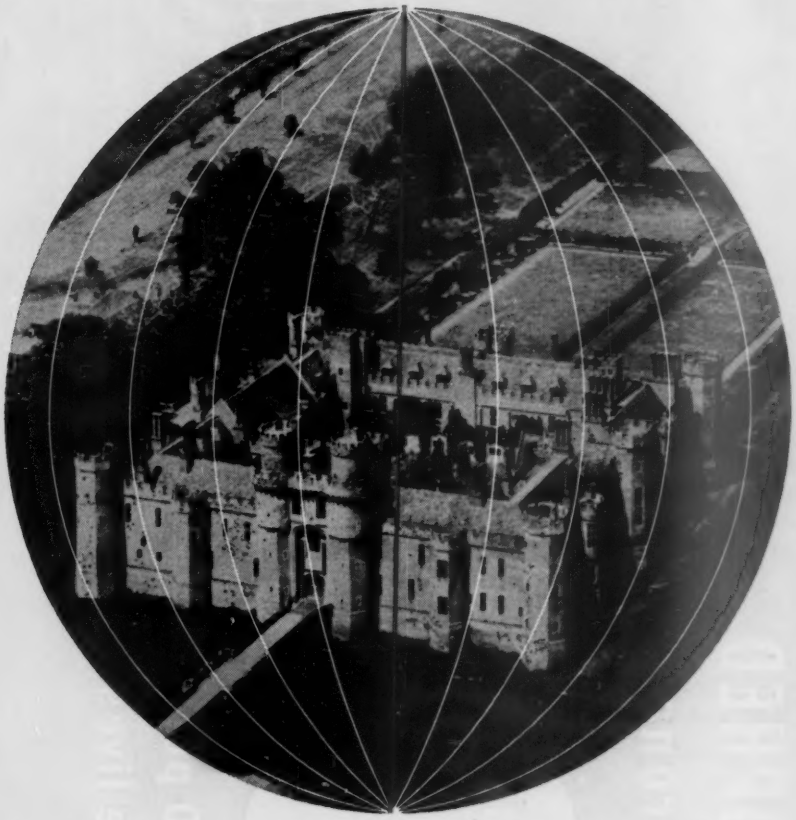


In medical science . . .
Penicillin continues to hold
its prime position.
It remains the accepted standard—
the antibiotic of choice in
approximately 72% of infectious disease.
Whenever oral penicillin is indicated—
oral BICILLIN sets a standard.
Its clinical dependability is assured
through resistance to gastric
destruction and optimal absorption.

The Greenwich Observatory marks the prime meridian of the earth. All time and space concepts of the globe are standardized from that point.

Wyeth
Philadelphia 1, Pa.

TABLETS SUSPENSION

BICILLIN®

Benzathine Penicillin G
(Dibenzylethylenediamine Dipenicillin G)

penicillin with a surety factor

LEVOPHED®
in coronary
shock
saves 20 per cent more lives[1]

Among 131 patients in **severe** shock due to myocardial infarction, Levophed saved the lives of 53[1] — a remarkable salvage rate where ordinarily there is an 80 to 90 per cent mortality rate.[2]

Intravenously administered Levophed is almost **twice** as effective in relieving shock and saving lives as expectant treatment — transfusions and older pressor agents.[1] "Survival occurred in two fifths of patients treated with levarterenol [Levophed] and in only one fifth of patients treated expectantly."[1]

Because delay may be disastrous[3] Levophed should be used **first** and promptly.

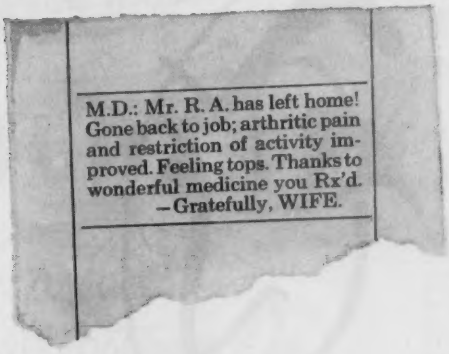
Levophed raises blood pressure within 10 to 30 seconds — maintains it almost indefinitely. Unlike other agents, Levophed produces an increase in coronary blood flow and oxygen supply to the myocardium far in excess of the rise in mean blood pressure.[4] Levophed limits the size of the infarct and saves healthy myocardium.[5]

LEVOPHED
(levarterenol bitartrate)
natural antishock pressor hormone

1. Binder, M. J., et al.: **Am. Jour. Med.**, 18:622, Apr., 1955. **2.** Sampson, J. J.; and Zipser, Albert: **Circulation**, 9:38, Jan., 1954. **3.** Nichol, E. S., in Conn, H. F.: Current Therapy 1954. Philadelphia, W. B. Saunders Co., 1954, p. 196. **4.** Jamison, W. L., et al.: **Jour. Am. Geriat. Soc.**, 3:521, Aug., 1955. **5.** Gilchrist, A. Rae: **Brit. Med. Jour.**, 2:351, Aug. 16, 1952.

Levophed (brand of levarterenol), trademark reg. U. S. Pat. Off.

Winthrop LABORATORIES • New York 18, N.Y. • Windsor, Ont.
(Formerly Winthrop-Stearns Inc.)


M.D.: Mr. R. A. has left home! Gone back to job; arthritic pain and restriction of activity improved. Feeling tops. Thanks to wonderful medicine you Rx'd.
—Gratefully, WIFE.

Sterane®
brand of prednisolone

Most active anti-rheumatic, anti-allergic, anti-inflammatory corticoid. White, scored 5 mg. tablets (bottles of 20 and 100) and pink, scored 1 mg. tablets (bottles of 100).

Pfizer **PFIZER LABORATORIES** Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York

Metamucil stimulates normal peristalsis *and* produces soft, easy stools.

"Smoothage" management with Metamucil may be continued as long as desired in every type of constipation.

METAMUCIL® SEARLE

psyllium hydrophilic mucilloid with dextrose

fresh mixed

Separate packaging of dry vitamins and diluent (mixed immediately before injection) assures the patient a more effective dose. May also be added to standard IV solutions.

FOLBESYN* B+C COMPLEX

VITAMINS LEDERLE

assures full potency

Dosage: 2 cc. daily.
Each 2 cc. dose contains:

Thiamine HCl (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	50 mg.
Pyridoxine HCl (B_6)	5 mg.
Sodium Pantothenate	10 mg.
Ascorbic Acid (C)	300 mg.
Vitamin B_{12}	15 mcgm.
Folic Acid	3 mg.

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LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK

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IN PEPTIC ULCER

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AMPHOJEL® double gel for biphasic action
ALUMINUM HYDROXIDE GEL

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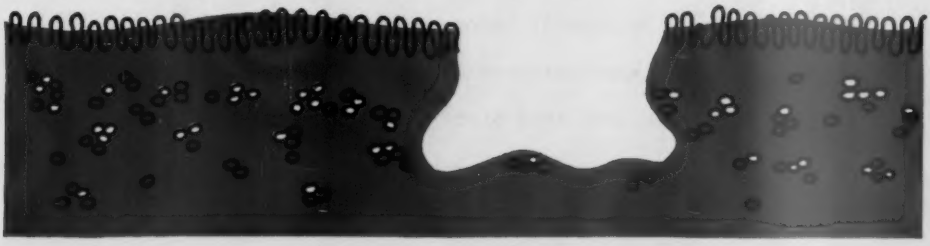
Philadelphia 1, Pa.



" . . . Well, I always prescribe Rorer's Maalox. It's an excellent antacid, doesn't constipate and patients will take it indefinitely."

MAALOX® suspension, bottles of 12 fluidounces *(sample on request)*; tablets, bottles of 100.

An efficient antacid suspension of magnesium-aluminum hydroxide gel; tablets, 0.4 Gm.

WILLIAM H. RORER, INC. 4865 Stenton Ave., Philadelphia 44, Pennsylvania

Please Mention this Journal when writing to Advertisers

Parkinson's disease

PANPARNIT®

hydrochloride

helps patients

to help themselves

Most distressing of all to the parkinsonian patient is his muscular rigidity... a pathologically imposed strait jacket that forces him to depend on others for many of his needs.

PANPARNIT... "the drug of choice" in 62 per cent* of cases... generally affords substantial relief of spasm, restoring the patient's ability to care for himself and boosting his morale. In many instances PANPARNIT also produces gratifying relief of tremor.

A gradually increasing schedule of dosage is recommended for optimal results.

*Schwab, R. S., and Leigh, D., J.A.M.A. *139*:629, 1949.

PANPARNIT® hydrochloride (caramiphen hydrochloride GEIGY). Sugar-coated tablets of 12.5 mg. and 50 mg.

GEIGY

Ardsley, New York

77487

there's no substitute for standardized testing

color-calibrated

CLINITEST®

BRAND

the urine-sugar test with the color scale that never varies

- **full color calibration**—standard blue-to-orange color scale does not omit the critical readings: ¾% (++); 1% (+++).
- **easy-to-read colors**—sharp distinctions give reliable readings, dependable reports.
- **uniformly reliable**—results you can trust, reports you can rely on.

AMES COMPANY, INC · ELKHART, INDIANA

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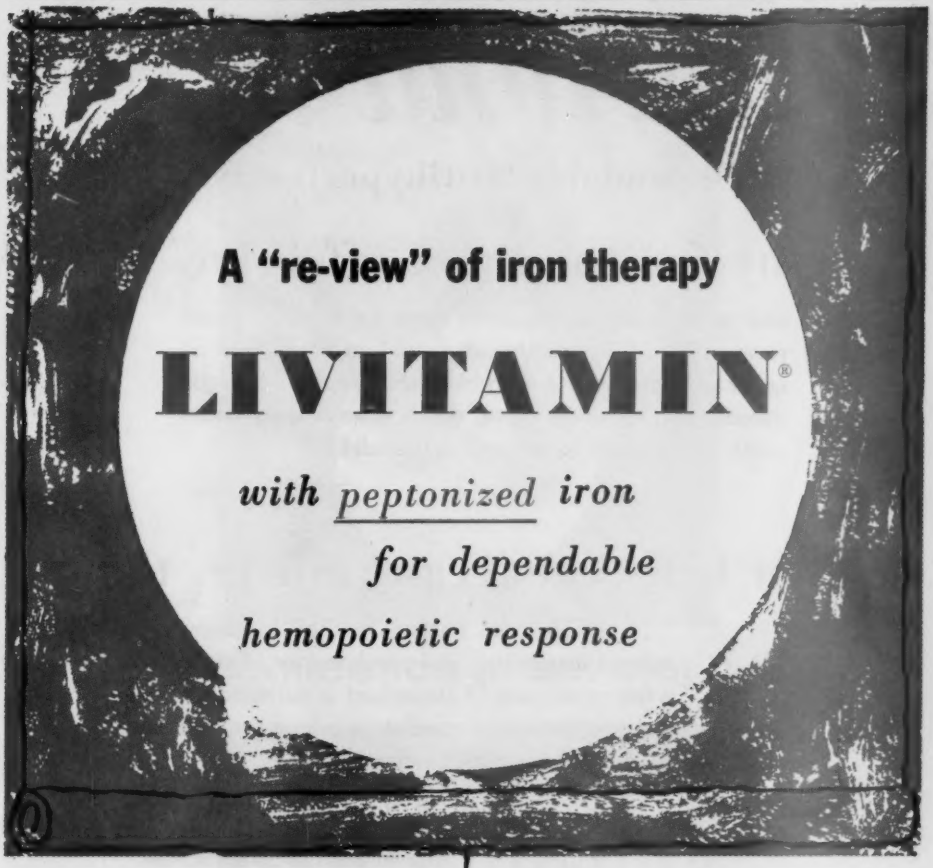


It is well-established that peptonized iron is virtually predigested. Anemias refractory to other forms of iron will often respond promptly to Livitamin. And the Livitamin formula, containing the B complex, provides integrated therapy to correct the blood picture, and to improve appetite and digestion.

Current studies* show Peptonized Iron
—One-third as toxic as ferrous sulfate.
—Absorbed as well as ferrous sulfate.
—Non-astringent.
—Free from tendencies to disturb digestion. (One-tenth as irritating to the gastric mucosa as ferrous sulfate.)
—Highly effective in iron-deficiency anemias.

*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate. Read before the American Association for the Advancement of Science, Atlanta, Georgia, December, 1955

EACH FLUIDOUNCE CONTAINS:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	0.42 Gm.
Manganese citrate, soluble	0.158 Gm.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Cobalamin Conc. (Vitamin B_{12} activity)	20 mcg.
Niacinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

The S. E. MASSENGILL Company
Bristol, Tennessee
New York Kansas City San Francisco

Rauwiloid®

A Dependable Antihypertensive

"...by far the most effective

and useful orally administered agent for reducing blood pressure . . . fully worthy of a trial in every case of essential hypertension in which treatment is thought necessary. The severe cases, which always need treatment, are as likely to respond as the mild."[1]

1. Locket, S.: Brit. M.J. *1*:809 (Apr. 2) 1955.

An Effective Tranquilizer, too

" . . . relief from anxiety resulted in generally increased intellectual and psychomotor efficiency with a few exceptions."[2] Rauwiloid is outstanding for its *nonsoporific* sedative action in a long list of diseases burdened by psychic overlay.

2. Wright, W.T., Jr., et al.: J. Kansas M. Soc. *57*:410 (July) 1956.

Dosage: Merely two 2 mg. tablets at bedtime. After full effect one tablet suffices.

A logical first step when more potent drugs are needed

Rauwiloid is recognized as basal medication in all grades and types of hypertension. In combination with more potent agents it proves synergistic or potentiating, making smaller dosage effective and freer from side actions.

Rauwiloid®+Veriloid®

In moderate to severe hypertension this single-tablet combination permits long-term therapy with dependably stable response. Each tablet contains 1 mg. Rauwiloid (alseroxylon) and 3 mg. Veriloid (alkavervir). Initial dose, 1 tablet t.i.d., p.c.

Rauwiloid®+ Hexamethonium

In severe, otherwise intractable hypertension this single-tablet combination provides smoother, less erratic response to hexamethonium. Each tablet contains 1 mg. Rauwiloid and 250 mg. hexamethonium chloride dihydrate. Initial dose, ½ tablet q.i.d.

Riker LOS ANGELES

For new confidence in antibiotic therapy

CATHOMYCIN®
SODIUM

(CRYSTALLINE SODIUM NOVOBIOCIN)

You may depend on CATHOMYCIN for rapid control of infections caused by *Staphylococcus* and *Proteus*, including those previously resistant to *all* clinically useful antibiotics. CATHOMYCIN is well tolerated by most patients, will not upset the gram-negative intestinal flora, and displays no cross resistance with other antibiotics. CATHOMYCIN in full dosage may be used in combination with other antibiotics where indicated.

Dosage: Two capsules (500 mg.) twice daily.

Supplied: CATHOMYCIN Sodium in capsules, each containing the equivalent of 250 mg. novobiocin, bottles of 16.

CATHOMYCIN is the trade-mark of Merck & Co., Inc.

MSD

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

NEW
BIOPAR® FORTÉ
TABLETS
• contain non-inhibitory intrinsic factor . . .
• permit optimal absorption of vitamin B_{12} at therapeutic dosage levels . . . orally

Biopar Forté Tablets contain the non-inhibitory intrinsic factor which is superior to ordinary intrinsic factor preparations. Biopar Forté provides the same rapid and intensive hemopoietic response as that obtained from injectable vitamin B_{12}. And due to the non-inhibitory intrinsic factor, this response is just as dependable.

Each Biopar Forté Tablet contains:
Vitamin B_{12} with Intrinsic Factor ½ U.S.P. Unit (Oral)*
Vitamin B_{12} (activity equivalent) 25 mcg.
Bottles of 30 tablets

*Unitage established prior to compounding

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY, KANKAKEE, ILLINOIS

in rheumatic fever...

The Telltale Heart

Carditis is a most serious manifestation of rheumatic involvement. It tells a tale of initial or recurrent streptococcal attack—of organic damage and grave dysfunction. To protect the heart from these consequences is a major objective of BICILLIN prophylaxis.

Recommended by the American Heart Association:[1]

- **To prevent rheumatic-fever onset**—treatment of streptococcal infections:

Children—One intramuscular injection of 600,000 to 900,000 units

Adults—One intramuscular injection of 900,000 to 1,200,000 units

- **To prevent rheumatic-fever recurrence**—prophylaxis of streptococcal infections:

Rheumatic-fever patients—One intramuscular injection monthly of 1,200,000 units

1. American Heart Association: Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis, Charles H. Rammelkamp, Chairman: Circulation *15*:154 (Jan.) 1957.

Wyeth® Philadelphia 1, Pa.

INJECTION BICILLIN® LONG-ACTING

Benzathine Penicillin G (Dibenzylethylenediamine Dipenicillin G), Wyeth

MANTLE OF PROTECTION

PHOTOGRAPH BY JIM BROWN

701063

Desbutal®

(DESOXYN® plus NEMBUTAL®)

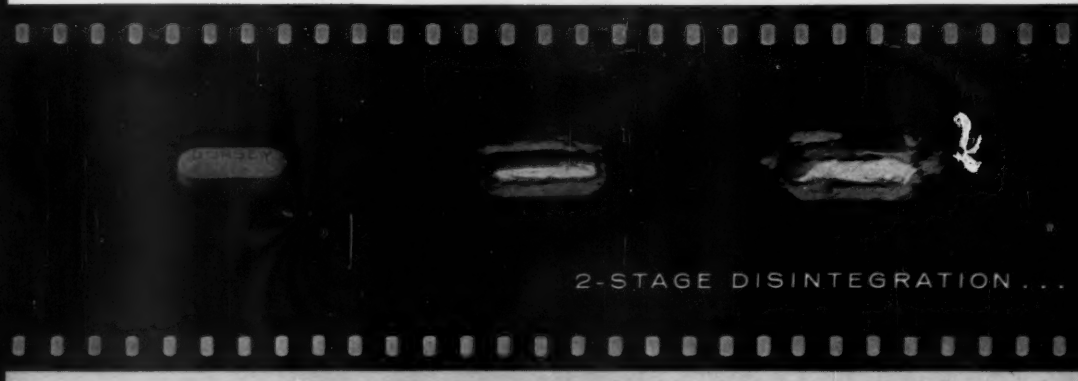
to dispel anxiety and depression

One capsule represents 5 mg. DESOXYN (Methamphetamine, Abbbott) Hydrochloride and 30 mg. NEMBUTAL (Pentobarbital, Abbott) Sodium.

Abbott

New...improved salicylate therapy

in a TANDEM RELEASE tablet



The outer layer of Buffered Pabirin Tablets quickly releases aluminum hydroxide for buffering action. PABA to potentiate acetylsalicylic acid and therapeutic doses of ascorbic acid to offset depletion are also in the outer layer.

The inner core of Buffered Pabirin Tablets containing acetylsalicylic acid alone begins to expand after the buffering action has started.

Arthritic patients—the very patients who need salicylate therapy most—are also the ones least able to tolerate salicylates over prolonged periods without gastric distress. This problem is now solved by the new Buffered Pabirin Products. The protective antacid (aluminum hydroxide) buffers against gastric irritation. PABA and the antacid potentiate acetylsalicylic acid and rapidly create high, sustained blood levels with low salicylate dosage...higher than with PABA or buffers alone. Studies show that high salicylate plasma levels promote an increase in production of adrenal cortical hormones.

For resistant rheumatics, Buffered Pabirin AC Tablets provide the added benefits of hydrocortisone. The use of hydrocortisone with acetylsalicylic acid reduces corticoid dosage to minimize the danger of adrenal atrophy. And PABA retards breakdown of hydrocortisone by the liver thereby prolonging its effect.

Buffered Pabirin and Buffered Pabirin AC Tablets are both sodium and potassium free.

SMITH-DORSEY • Lincoln, Nebraska • a division of The Wander Company

☆ buffered for superior gastric tolerance

☆ buffered for faster pain relief

RESULT:

The inner core then disintegrates rapidly and permits fast absorption of the acetyl salicylic acid.

Buffered Pabirin AC Tablets release, in addition, hydrocortisone from the core.

- increased range of motion
- faster pain relief
- superior gastric tolerance

for most rheumatoid arthritics

Buffered Pabirin® TABLETS

300 mg.	Acetylsalicylic acid (5 gr.)	300 mg.
300 mg.	Para-aminobenzoic acid (5 gr.)	300 mg.
50 mg.	Ascorbic acid	50 mg.
100 mg.	Dried aluminum hydroxide gel	100 mg.

Dosage: Two or three tablets 3 or 4 times daily. In rheumatic fever three to five tablets 4 or 5 times daily.

for resistant rheumatics

Buffered Pabirin®-AC TABLETS

2.5 mg.	Hydrocortisone	
300 mg.	Acetylsalicylic acid (5 gr.)	
300 mg.	Para-aminobenzoic acid (5 gr.)	
50 mg.	Ascorbic acid	
100 mg.	Dried aluminum hydroxide gel	

Dosage: Initially, one or two tablets 4 times daily, after meals and on retiring. Reduction of dosage should be gradual; never stopped abruptly.

to minimize straining at stool...

Colace

DIOCTYL SODIUM SULFOSUCCINATE, MEAD JOHNSON*

softens stools for easy passage

without laxative action · without adding bulk

By its surface-active properties, Colace increases the wetting efficiency of intestinal water and promotes the formation of oil-water emulsions. Thus Colace keeps stools normally soft, and softens already hardened stools, for easy, natural passage.

Colace provides a new approach in the management of constipation. In patients with cardiac conditions, it prevents or greatly reduces straining at stool. Gentle and nonlaxative, Colace does not cause drastic emptying or overfrequent bowel movements. No undesirable side effects have been reported.

MEAD JOHNSON

SYMBOL OF SERVICE IN MEDICINE

SUGGESTED ORAL DAILY DOSAGE

Adults and older children	50 to 200 mg.
0 to 3 years	10 to 40 mg.
3 to 6 years	20 to 60 mg.
6 to 12 years	40 to 120 mg.

THE COLACE FAMILY

NEW Colace Capsules 100 mg., bottles of 30, 60 and 250.

Colace Capsules 50 mg., bottles of 30, 60 and 250.

Colace Liquid (1% solution; 10 mg. per cc.), 30 cc. bottles with calibrated dropper.

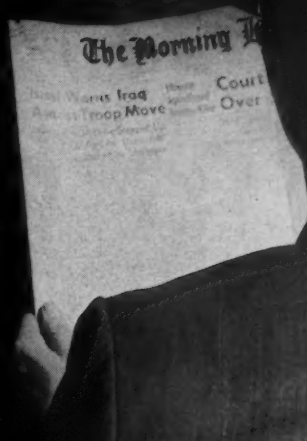
NOW Colace Syrup (an orange- and mint-flavored aqueous solution; 20 mg. per teaspoon), 8 ounce bottles.

*Patents pending

13667

to quiet the cough

and calm the patient . . .



THROUGH THE DAY

THROUGH THE NIGHT

Expectorant action
Antihistaminic action
Sedative action
Topical anesthetic action

PHENERGAN

EXPECTORANT

Promethazine Expectorant with Codeine · Plain (without Codeine)

Wyeth
Philadelphia 1, Pa.

The Well-Proportioned Nutrients in Enriched Bread

Equally Important in the Diet Adjusted for Gout and Gouty Arthritis

ENRICHED BREAD presents the fortunate combination of richness in many essential nutrients and negligible content of purines. This combination qualifies it eminently as an important food in the diet called for in gout and gouty arthritis. It has an equally justified place in both the "purine-free" diet recommended during acute attacks and in the purine-low diet advised during symptomless intervals.

The added nutrients of enriched bread are selected qualitatively and quantitatively because of their importance in everyday nutrition. They have proved especially important in restricted diets.

It is now advocated that the diet of patients with gout should also be low in fat, because fats purportedly inhibit purine excretion. The low fat content of enriched bread (approximately 3 per cent), together with its blandness, low bulk, and easy digestibility, proves advantageous in the diet of the gouty patient.

Six slices of average enriched bread per day provide 12 grams of protein, 0.36 mg. of thiamine, 0.26 mg. of riboflavin, 3.35 mg. of niacin, 3.5 mg. of iron, and 126 mg. of calcium. These amounts contribute from 16 to 29 per cent of the patient's daily nutritional needs of each of these essentials, yet represent only 378 calories, barely 19 per cent of the nutrient energy of a 2,000 calorie diet.

AMERICAN BAKERS ASSOCIATION

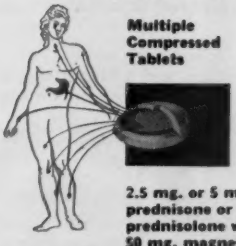
20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

clinical evidence[1,2,3] indicates that to augment the therapeutic advantages of the "predni-steroids" antacids should be routinely co-administered to minimize gastric distress

ROUTINE CO-ADMINISTRATION MEANS

'Co-Hydeltra'
(Prednisolone Buffered)



Multiple Compressed Tablets

2.5 mg. or 5 mg. prednisone or prednisolone with 50 mg. magnesium trisilicate and 300 mg. aluminum hydroxide gel.

'Co-Deltra'
(Prednisone Buffered)

All the benefits of the "predni-steroids" plus positive antacid action to minimize gastric distress.

References: 1. Boland, E. W., *J.A.M.A.* 160:613 (February 25) 1956. 2. Margolis, H. M. *et al.*, *J.A.M.A.* 158:454 (June 11) 1955. 3. Bollet, A. *J. et al.*, *J.A.M.A.* 158:459 (June 11) 1955.

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MERCK SHARP & DOHME
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PHILADELPHIA 1, PA.

'CO-DELTRA' *and* 'CO-HYDELTRA' *are trademarks of* MERCK & CO., INC.

Medihaler®

For the Asthmatic

Fast Relief

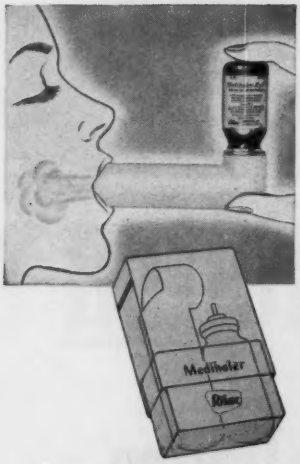
Medihaler offers virtually instantaneous relief and does so with little effort and with maximum safety.

Measured-Dose True Nebulization

Delivers a measured dose of true nebular vapor... Dose is always the same regardless of strength of fingers or amount of medication in bottle.

Costs the Patient Less

Medihaler Oral Adapter is made of unbreakable plastic ...no moving parts...and 200 applications in each 10 cc. bottle.



Medihaler-Epi®

Riker brand of epinephrine U.S.P. 0.5% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.125 mg. epinephrine. In 10 cc. vial with metered-dose valve.

Indicated in acute or recurring bronchospasm. Replaces injected epinephrine in many emergency situations.

Medihaler-Iso®

Riker brand of isoproterenol HCl 0.25% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.06 mg. isoproterenol. In 10 cc. vial with metered-dose valve. • Indicated in acute or recurring bronchospasm.

***Note:** First prescription should include desired medication and Medihaler Oral Adapter, supplied with pocket-sized plastic container.*

The Medihaler principle

is also available in Medihaler-Nitro™ (octyl nitrite) for the rapid relief of angina pectoris... and Medihaler-Phen™ (phenylephrine-hydrocortisone-neomycin) for lasting, effective relief of nasal congestion.

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among nonhormonal antiarthritics...
unexcelled in
therapeutic potency

BUTAZOLIDIN®

in the nonhormonal treatment of arthritis and allied disorders no agent surpasses BUTAZOLIDIN in potency of action.

Its well-established advantages include remarkably prompt action, broad scope of usefulness, and no tendency to development of drug tolerance. Being nonhormonal, BUTAZOLIDIN causes no upset of normal endocrine balance.

BUTAZOLIDIN relieves pain, improves function, resolves inflammation in:
Gouty Arthritis
Rheumatoid Arthritis
Rheumatoid Spondylitis
Painful Shoulder Syndrome

BUTAZOLIDIN being a potent therapeutic agent, physicians unfamiliar with its use are urged to send for detailed literature before instituting therapy.

BUTAZOLIDIN® (phenylbutazone GEIGY). Red coated tablets of 100 mg.

GEIGY
Ardsley, New York

There is a distinctive A

on every

Armour Thyroid Tablet

it symbolizes an unsurpassed preparation for thyroid therapy

A® THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS

on your prescriptions

SPECIFY

ARMOUR thyroid

THESODATE

THE ORIGINAL ENTERIC-COATED TABLET
OF THEOBROMINE SODIUM ACETATE

provides
EFFECTIVE
WELL-TOLERATED
PROLONGED
VASO-DILATION

REPEATEDLY SHOWN and proven by objective tests on human subjects[1] — this is one of the most effective of all the commonly known Xanthine derivatives. Because of the enteric coating it may be used with marked freedom from the gastric distress characteristic of ordinary Xanthine therapy. Thus **THESODATE**, with its reasonable prescription price also, enjoys a greater patient acceptability.

in
CORONARY
ARTERY
DISEASE

Available: **In bottles of 100, 500, 1000.**

TABLETS THESODATE

***(7½ gr.) 0.5 Gm. *(3¾ gr.) 0.25 Gm.**

THESODATE WITH PHENOBARBITAL

***(7½ gr.) 0.5 Gm. with (½ gr.) 30 mg.**
(7½ gr.) 0.5 Gm. with (¼ gr.) 15 mg.
***(3¾ gr.) 0.25 Gm. with (¼ gr.) 15 mg.**

THESODATE WITH POTASSIUM IODIDE

(5 gr.) 0.3 Gm. with (2 gr.) 0.12 Gm.

THESODATE, POTASSIUM IODIDE WITH PHENOBARBITAL

(5 gr.) 0.3 Gm., (2 gr.) 0.12 Gm. with (¼ gr.) 15 mg.

***In capsule form also, bottles of 25 and 100.**

1. Riseman, J. E. F. and Brown, M. G. Arch. Int. Med. 60: 100, 1937
2. Brown, M. G. and Riseman, J. E. F. JAMA 109: 256, 1937.
3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

For samples just send your Rx blank marked — 7-TH-3

Brewer EST. 1852

BREWER & COMPANY, INC. WORCESTER 8, MASSACHUSETTS U.S.A.

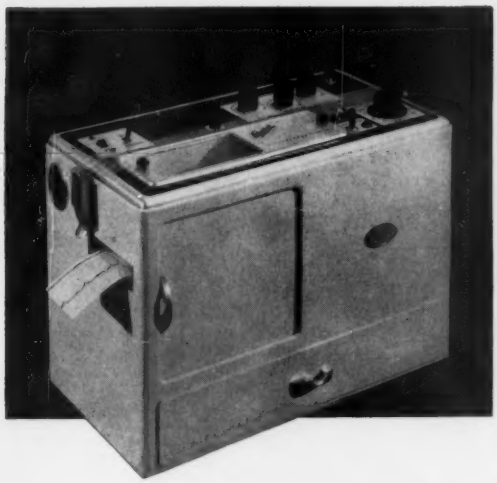
Dexamyl* (a combination of dextro-amphetamine sulfate, S.K.F., and amobarbital) induces a mood of cheerfulness and optimism. Often, this is all that is needed to help the aged overcome their loneliness, the resentful feeling of being unwanted, the fears (imagined or real) of physical failings.

tablets—elixir—Spansulet capsules

smooth and subtle encouragement for the aged

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.
†T.M. Reg. U.S. Pat. Off. for sustained release capsules. S.K.F.



Essential Criteria in Electrocardiograph Performance

- **ACCURACY**
- **SIMPLICITY**
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The BURDICK Electrocardiograph

The Burdick Electrocardiograph consistently delivers an immediate, clear and permanent straight-line tracing. Leads are selected at the turn of a dial and there is no delay or base line shift between leads. You can use this instrument with full confidence in your office or in the home. The sturdy, compact cabinet and the operating mechanism inside are built to withstand the uncertainties of automobile transportation and fluctuations in temperature and humidity.

Ask your Burdick dealer for a demonstration

THE BURDICK CORPORATION Burdick MILTON, WISCONSIN

Most patients treated with 'Compazine'. . .
"showed prompt, marked improvement in their emotional outlook."

Vischer[1] reports that 37 of 38 patients treated with 'Compazine' for psychoneurotic symptoms had "marked" or "moderate" relief. "21 patients were totally free of such symptoms and obtained a better response than to any previous medication. Confusion and depression disappeared dramatically, and primary complaints became less important to them as they became far more relaxed, less nervous and less tense. Many were able to return to work or had renewed interest in their surroundings and hobbies."

1. Vischer, T.J.: Clinical Study of Proclorperazine, A New Tranquilizer for the Treatment of Non-Hospitalized Psychoneurotics, New England J. Med., January, 1957.

Smith, Kline & French Laboratories, Philadelphia

Compazine★

a true tranquilizing agent with minimal side effects

★Trademark for proclorperazine, S.K.F.

Ann Woodward
Director

Dr. X Postponed His Vacation— —TOO LONG!

You've heard the story often. He simply could not get away: patients crowded in in unaccountable numbers; he couldn't leave Mr. Doe to someone else after the long struggle to save him, etc. etc.

But Dr. X unfortunately overlooked a thoroughly workable solution of his problem—help from a competent medical personnel bureau in finding an assistant, temporary *or* permanent. The Woodward Bureau gives swift, systematic service in situations like that of Dr. X. Many fine men in internal medicine and other fields announce their availability through our channels, and our background of over fifty years' experience in medical placement has alerted us to careful interpretations of individual needs.

Whether your requirements are immediate or long range, we are prepared to help you in finding medical personnel. Simply write, wire or phone . . .

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VASCUTUM® improved

the only lipotropic-antihemorrhagic with Quercetin

combats capillary fault—important contributor to mortality in hypertensive disease[1,2]
...reducing the 815% excessive mortality rate of hypertensives by as much as 76%[1-3]
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VASCUTUM improved Each Capsule contains:

Choline bitartrate	349 mg.
Inositol (anhydrous)	167 mg.
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Pyridoxine HCl	0.67 mg.
Quercetin	15 mg.
Ascorbic acid	12.5 mg.
Vitamin B_{12}	2 mcg.

Suggested dosage: One capsule q.i.d.
Supplied: Bottles of 100 and 1,000 hard gelatin capsules.

(1) Griffith, J. Q., Jr.; Naghski, J., and Krewson, C. F.: Rutin and Related Flavonoids, Boston, Pa., Mack Publishing Co., 1953. (2) Griffith, J. Q., Jr.; Datta, P.; Naghski, J., and Krewson, C. F.: A.M.A. Arch. Int. Med. 94:1037, 1954. (3) Griffith, J. Q., Jr.: Ib. Clin. North America 20:1717, 1954.

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The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Tuition fees for all courses will be: Members, $30.00; Non-members, $60.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa.

	March				April						May				June			
	4–8	11–15	18–22	25–29	1–5	8–12	15–19	22–26	29–M 3		6–10	13–17	20–24	27–31	3–7	10–14	17–21	24–28
Course No. 1, PATHOLOGY AND PATHOLOGIC PHYSIOLOGY IN INTERNAL MEDICINE: The Frank E. Bunts Institute of the Cleveland Clinic Foundation, Cleveland, Ohio; A. Carlton Ernstene, M.D., F.A.C.P., Director.				X														
Course No. 2, GASTRO-ENTEROLOGY: Boston University School of Medicine, Boston, Mass.; Franz J. Ingelfinger, M.D., F.A.C.P., Director.					X													
Course No. 3, INTERNAL MEDICINE: The University of Chicago Department of Medicine, Chicago, Ill.; Wright Adams, M.D., F.A.C.P., Director, and Robert G. Page, M.D., Co-director.												X						
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Course No. 6, CARDIOLOGY: The National Institute of Cardiology of Mexico, Mexico, D. F.; Ignacio Chávez, M.D., F.A.C.P., Director.														X				
Course No. 7, INTERNAL MEDICINE: New York University Post-Graduate Medical School, New York, N. Y.; Charles F. Wilkinson, Jr., M.D., F.A.C.P., and Clarence E. de la Chapelle, M.D., F.A.C.P., Co-directors.														X				
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A.C.P. Annual Session, Boston, Mass.

A.M.A. Annual Meeting, New York, N. Y.

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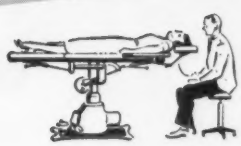

Horizontal

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Consider these energy-saving features—quietly powerful motor-hydraulic base for effortless, full 18" patient elevation; smooth hand wheel tilt; 180 degree rotation; 7-position rectangular headrest cushion; combination kneerest, footrest and table top extension; self-energizing automatic hand lever locks for back and leg sections.

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- Methamphetamine for its anorexigenic and mood-lifting effects.
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1. Eisfelder, H.W.: Am. Pract. & Dig. Treat. 5:778 (Oct., 1954)

2. Sebrell, W.H., Jr.: J.A.M.A. 152:42 (May, 1953)

3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954)

Write for 60-10-70 Menu pads, weight charts and samples of Obedrin

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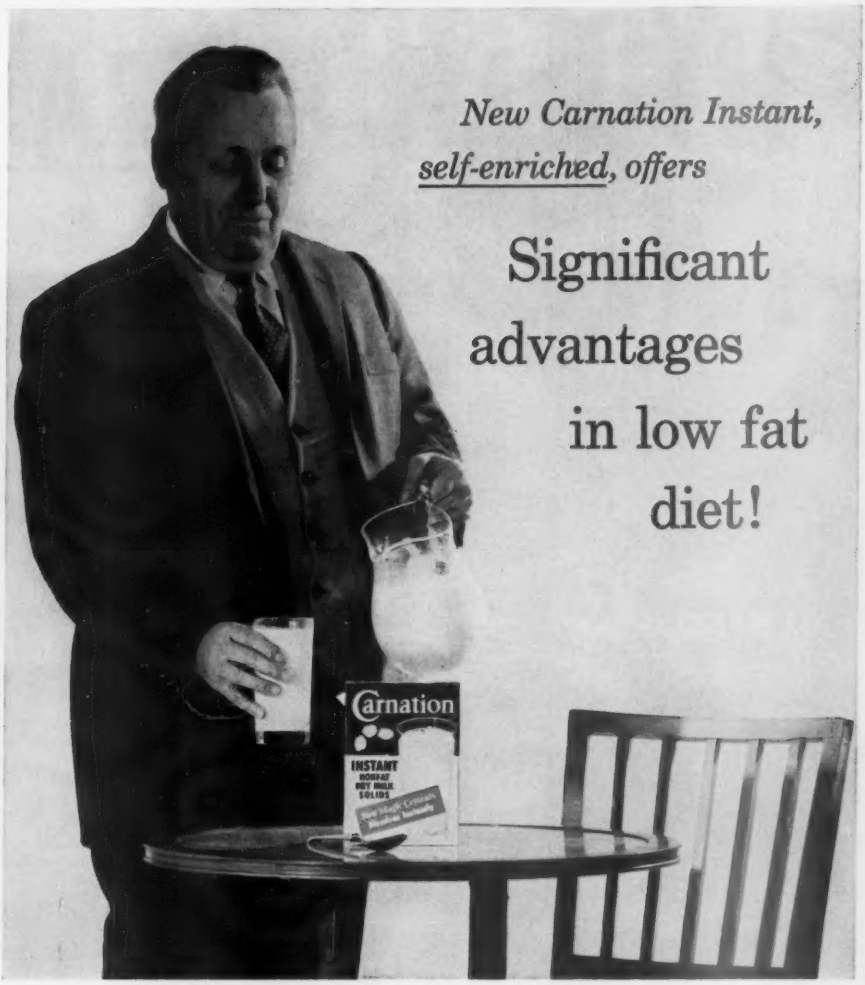

1/4 more protein, richer flavor than ordinary nonfat milk!

Carnation Instant, new *crystal form* of nonfat milk brings a *new* dietary advantage – delicious *self-enriched* nonfat milk. One extra tablespoon per glass, or ⅓ cup *extra* crystals per quart, provides richer flavor and significant nutritional advantages compared to the usual nonfat milk.

CONVENIENT. Mixes instantly and completely in ice-cold water with a light stir. Ready to drink, at home or away from home, with delicious fresh flavor.

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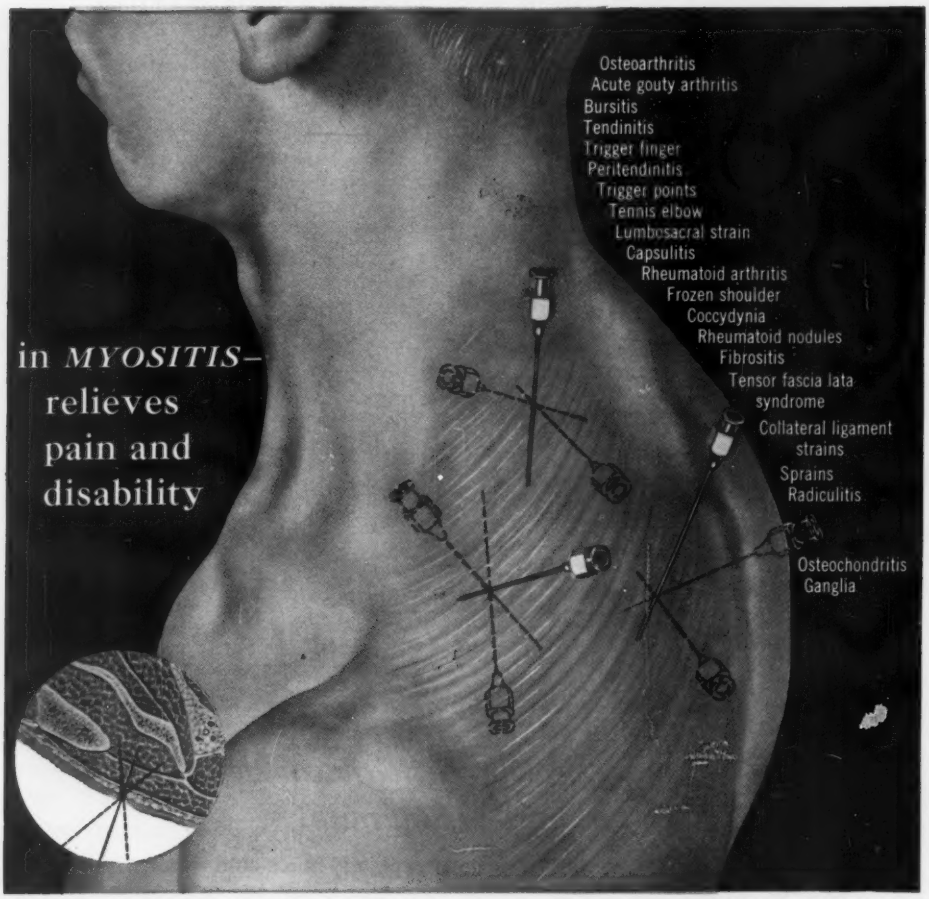
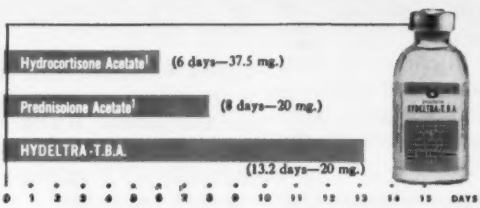
HYDELTRA® -T.B.A.

(Prednisolone *tertiary*-butylacetate, Merck)

for relief that lasts—longer



Anti-inflammatory effect lasts longer than that provided by any other steroid ester


Hydrocortisone Acetate[1] (6 days—37.5 mg.)
Prednisolone Acetate[1] (8 days—20 mg.)
HYDELTRA-T.B.A. (13.2 days—20 mg.)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 DAYS

Dosage: the usual intra-articular, intra-bursal or soft tissue dose ranges from 20 to 30 mg. depending on location and extent of pathology.

Supplied: Suspension 'HYDELTRA'-T.B.A.—20 mg./cc. of prednisolone *tertiary*-butylacetate, in 5-cc. vials.

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DIVISION OF MERCK & CO., INC.
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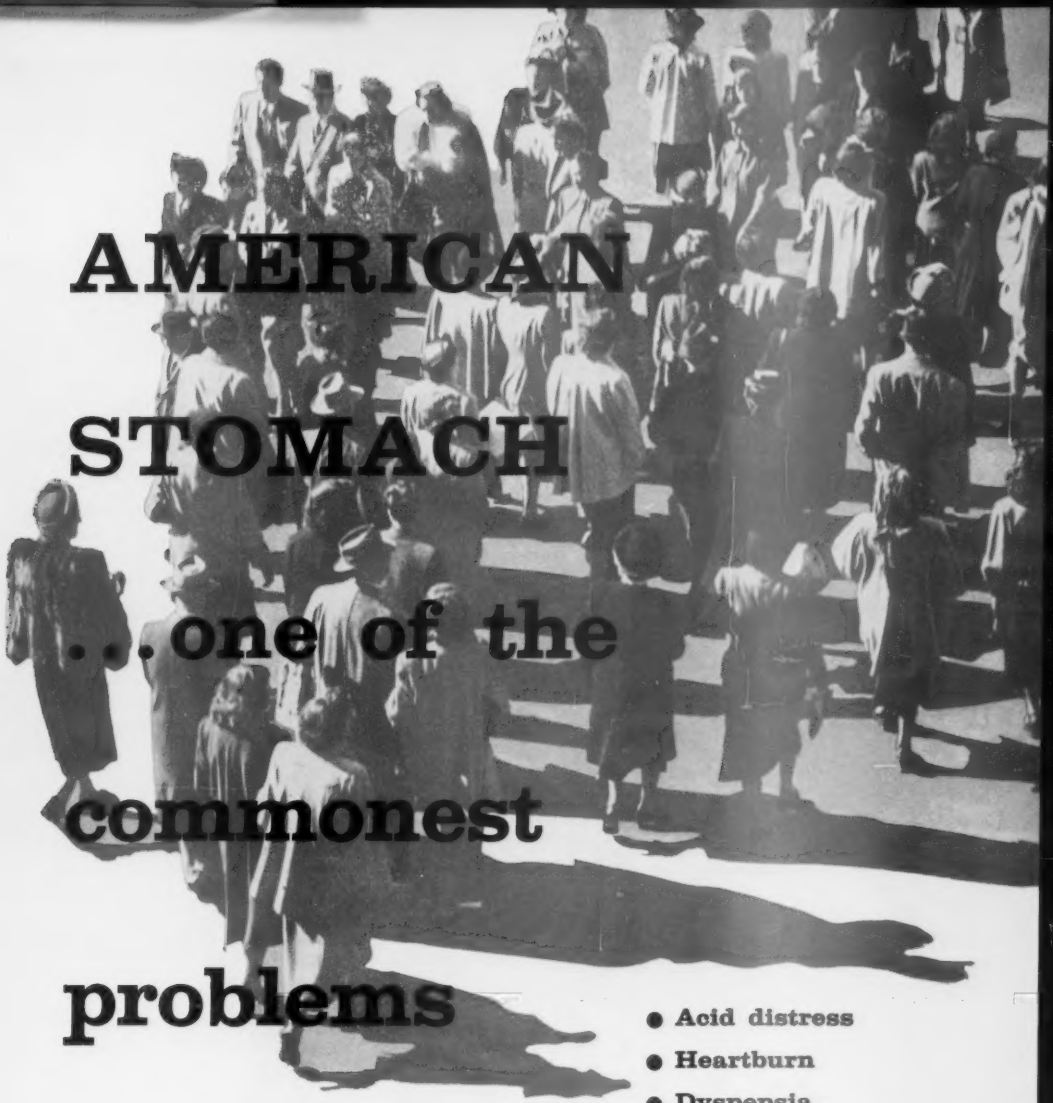
1. Hollander, J. L., *Paper read at conference in New York City, May 31 and June 1, 1955*



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- **Acid distress**
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"American Stomach" describes the familiar gastric stress in today's pattern of excesses and tension. For these hyperacid states, ALUDROX offers modern control with its *balanced* antacid action. Prescribe it for prompt and prolonged buffering without constipation, acid rebound, or alkalosis.

NEW—*Peppermint-Flavored Suspension*

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to neutralize, not penalize

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With two doses a day

Lipo Gantrisin 'Roche'—a new, palatable liquid for antibacterial therapy—offers three significant features:

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Relieves the pain where it hurts: the gut

2 caps t.i.d.

1. Hardin, J. H.; Levy, J. S., and Seager, L.: South. M. J. 47:1190.1954.

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TRADEMARK: "BENTYL"

Mom "wears
the pants"
once too
often

frozen shoulder

Bursitis and tenosynovitis are new terms to homemakers, but they are not uncommon sequels to overexertion. Early antirheumatic therapy is to be encouraged in the treatment of these conditions, as it is in more serious rheumatic conditions, to alleviate pain and prevent progression of the disorder. With adequate therapy the prognosis of bursitis in its acute stage is good. Delaying therapy may result in extension of the inflammation and gross anatomical changes that tend to incapacitate the patient.

SIGMAGEN provides doubly protective corticoid-salicylate therapy—a combination of METICORTEN® (prednisone) and acetylsalicylic acid providing additive antirheumatic benefits as well as rapid analgesic effect. These benefits are supported by aluminum hydroxide to counteract excess gastric acidity and by ascorbic acid, the vitamin closely linked to adrenocortical function, to help meet the increased need for this vitamin during stress situations.

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SIGMAGEN*

corticoid-analgesic compound Tablets

for patients who go beyond their physical capacity

Schering

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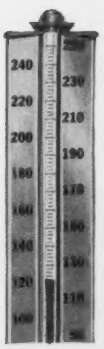
. . . from incapacitating hypertension to a life of usefulness.

Case History:[1] A.B., 42-year-old hospitalized patient with severe hypertension and early heart failure. Blood pressure prior to treatment was 240/160 mm. Hg. ANSOLYSEN was administered orally t.i.d. The dose was adjusted to the patient's requirements. Blood pressure was reduced to, and stabilized at, an average level of 150/105 mm. Hg. There was marked symptomatic improvement, and the patient was able to return to work.

1. Case history on file in Medical Department of Wyeth Laboratories.



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Lowers Blood Pressure

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...reduces risk in reducing

A totally new development in anorexigenic therapy, PRELUDIN substantially reduces the risks and discomfort in reducing.

Distinctive in its Chemistry: PRELUDIN is a totally new compound of the oxazine series.

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Distinctive in Tolerance: With PRELUDIN there is a notable absence of palpitations or nervous excitement. It may generally be administered with safety to patients with diabetes or moderate hypertension.

For your patient's greater comfort: PRELUDIN curtails appetite without destroying enjoyment of meals...causes a mild evenly sustained elevation of mood that keeps the patient in an optimistic and cooperative frame of mind.

Recommended Dosage: One tablet two or three times daily taken one hour before meals. Occasionally smaller dosage suffices.

PRELUDIN® (brand of phenmetrazine hydrochloride). Scored, square, pink tablets of 25 mg.
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NEW...

Each Multiple Compressed Tablet of MEPROLONE provides the inseparable antiarthritic, antirheumatic benefits of:

1. *Prednisolone buffered*—the newest and most potent of the "predni-steroids" for prompt relief of joint pain and arrest of the destructive inflammatory process.

2. *Meprobamate*—the newest and safest of the muscle-relaxant tranquilizers for profound relaxation of skeletal muscle in spasm.

Tolerance to this combination is good because there is little likelihood of sodium retention, potassium depletion or gastric distress with buffered prednisolone, and meprobamate rarely produces significant side effects in therapeutic dosage.

An additional important therapeutic benefit, often overlooked, stems from the tranquilizing action of meprobamate. This component of MEPROLONE relieves mental tension and anxiety so often manifest in arthritics, making them more amenable to other rehabilitation measures.

INDICATIONS: A wide variety of conditions, in which four symptoms predominate: *a*) inflammation *b*) muscle spasm *c*) anxiety and tension *d*) discomfort and disability; i.e., rheumatoid arthritis, rheumatoid spondylitis (Marie-Strümpell disease), Still's disease, psoriatic arthritis, osteoarthritis, bursitis, synovitis, tenosynovitis, myositis, fibrositis, fibromyositis, neuritis, acute and chronic low back pain, acute and chronic primary and secondary fibrositis and torticollis, intractable asthma, respiratory allergies, allergic and inflammatory eye and skin disorders (as maintenance therapy in disseminated lupus erythematosus, periarteritis nodosa, dermatomyositis and scleroderma).

Therapeutic benefits of MEPROLONE compared with traditional antiarthritics.

	relieves pain	suppresses inflammation	relaxes muscle	eases anxiety	imparts sense of well-being
Salicylates	✓	✓			
Muscle relaxants			✓[1]		
Tranquilizers				✓[1]	
Steroids	✓	✓			✓
MEPROLONE	✓	✓	✓	✓	✓

1. Meprobamate is the only tranquilizer with muscle-relaxant action.

SUPPLIED: Multiple Compressed Tablets in bottles of 100 in two formulas as follows: MEPROLONE-1—1.0 mg. of prednisolone, 200 mg. of meprobamate and 200 mg. of dried aluminum hydroxide gel. MEPROLONE-2—provides 2.0 mg. of prednisolone in the same formula.

NO OTHER

ANTIRHEUMATIC

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PROVIDES AS MANY

BENEFITS AS

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MEPRO PREDNISO | BAMATE LONE, *buffered*

THE ONLY

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ANTIARTHRITIC

THAT SIMULTANEOUSLY

RELIEVES:

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2. JOINT INFLAMMATION
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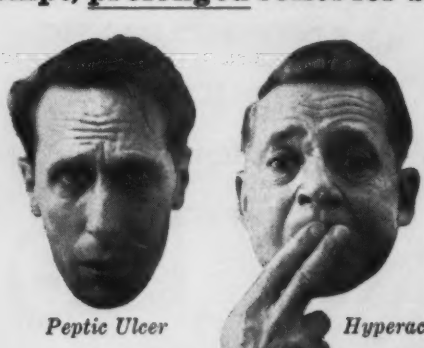
prompt, prolonged relief for both



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Kolantyl

Kolantyl provides four beneficial actions that relieve pain and correct a range of gastric disorders characterized by spasm and low pH.

1. Acid neutralization; 2. Relief of spasm and hypermotility by musculotropic and neurotropic inhibition; 3. Inactivation of pepsin and lysozyme; 4. Formation of a protective demulcent.

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Kolantyl

Gel and Tablets

Action:

Two-way spasmolysis . . . Spasm is relieved and gastric hypermotility is checked by the musculotropic and neurotropic effects of *Bentyl**—more effective than atropine, without the usual side effects.[1]

Rapid, Prolonged Antacid Effects[2] Balanced antacids act swiftly...do not cause laxation or constipation.

Demulcent Protection[3] . . . Normal tissue is safeguarded, and physiologic repair of damaged areas is enhanced.

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Each 10 cc. (2 teaspoonfuls) of Kolantyl Gel or each Kolantyl Tablet contains:

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Aluminum Hydroxide Gel	400 mg.
Magnesium Oxide	200 mg.
Sodium Lauryl Sulfate	25 mg.
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Dosage:

Gel—2 to 4 teaspoonfuls every three to four hours, or as needed.

Tablets—2 tablets (chewed for more rapid action) every three hours, or as needed.

Supplied:

Gel—12 oz. bottles. *Tablets*—bottles of 100 and 1,000.

*Merrell's distinctive antispasmodic that provides direct, fast relief of G. I. spasm and pain.

1. McHardy, G., and Browne, D.: South. M. J. 45:1139, 1952. 2. Hufford, A. R.: Rev. Gastroenterol. 18:588, 1951. 3. Johnston, R. L.: J. Indiana St. M. A. 46:869, 1953. 4. Miller, B. N.: J. South Carolina M. A. 48:345, 1952.

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BENNETT ***Flow Sensitive*** *VALVE*

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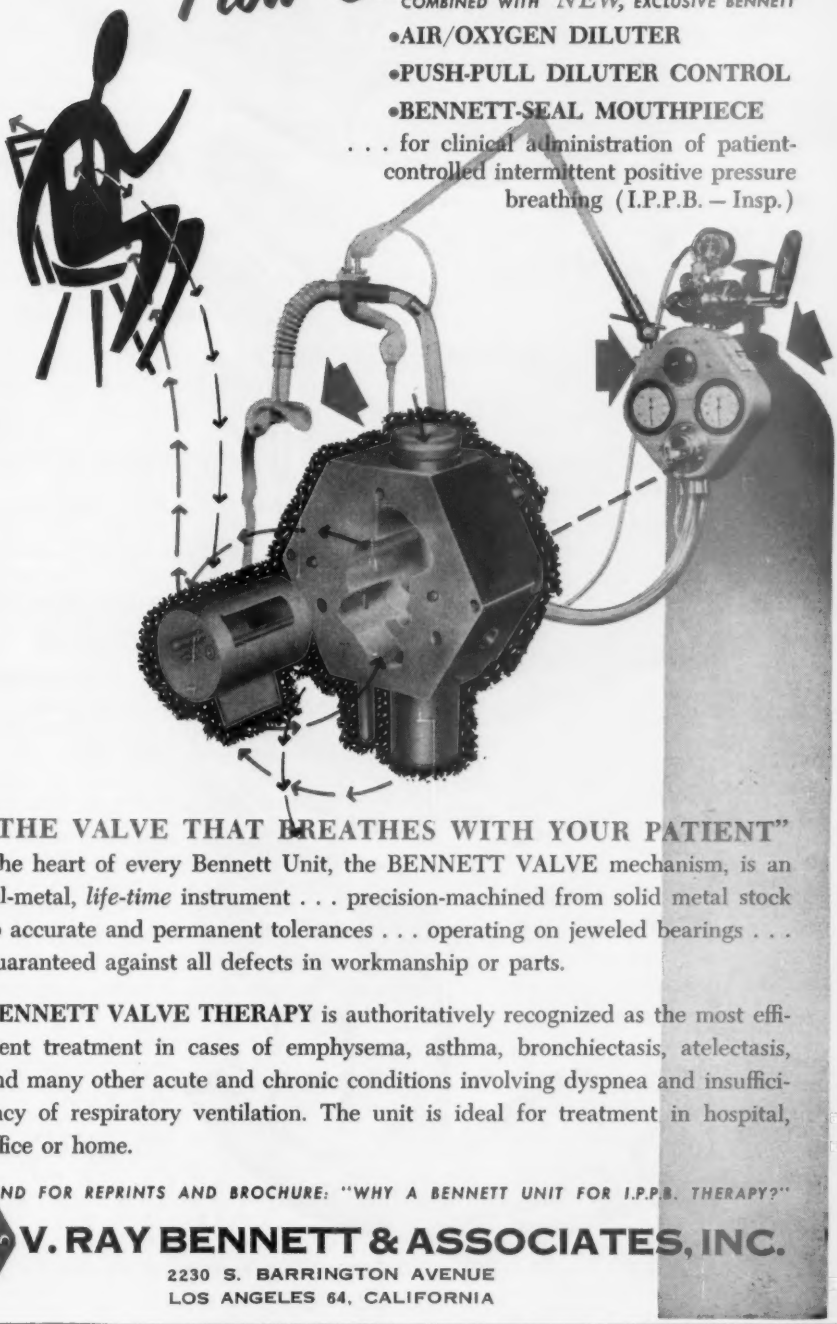
- **AIR/OXYGEN DILUTER**
- **PUSH-PULL DILUTER CONTROL**
- **BENNETT-SEAL MOUTHPIECE**

. . . for clinical administration of patient-controlled intermittent positive pressure breathing (I.P.P.B. – Insp.)



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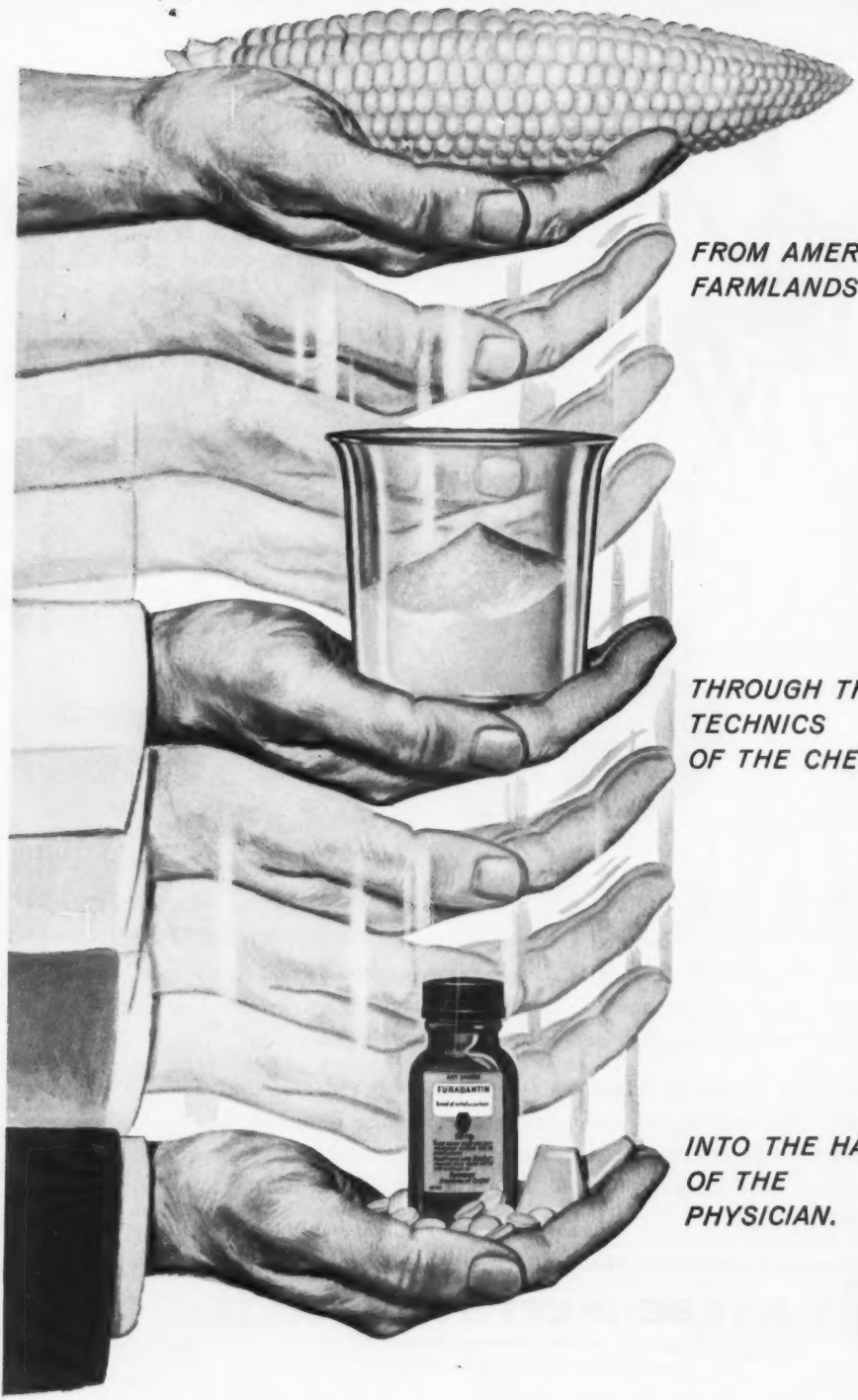

FROM AMERICA'S FARMLANDS...

THROUGH THE TECHNICS OF THE CHEMIST...

INTO THE HANDS OF THE PHYSICIAN.

The discovery in 1944 of a unique class of antimicrobial agents has placed a number of valuable new drugs in the hands of the physician. Utilizing such farm products as corncobs and oat hulls as a source of pentose and ultimately of furfural Eaton Laboratories developed a new group of synthetic organic compounds: the NITROFURANS.

NITROFURANS are taking their place alongside the sulfonamides and antibiotics as a major class of antimicrobial agents. They possess important and distinctive characteristics:

- bactericidal rather than bacteriostatic action
- effective against a wide range of gram-negative and gram-positive organisms
- a low order of toxicity for mammalian tissues
- negligible development of bacterial resistance
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- effective in the presence of blood, pus and serum
- no tendency to cause fungal superinfection
- stable

Over 417 different NITROFURANS now have been synthesized by Eaton Laboratories. Since the discovery of their antimicrobial properties in 1944,* over 1,300 articles on the biologic and therapeutic activity of these compounds have been published in 21 languages.

These NITROFURANS have far-reaching possibilities which have only begun to be realized. Some have anesthetic properties; others are antihistaminic; a few appear to have an effect upon a certain type of cancer; several may prove virucidal or vermicidal.

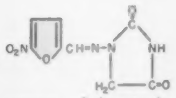
As organisms sensitive to antibiotics are replaced by strains of resistant bacteria, such new wide-spectrum chemotherapeutic agents with minimal toxicity as the NITROFURANS become increasingly important.

The Nitrofurans In Medicine

FURADANTIN®

BRAND OF NITROFURANTOIN

for genitourinary infections



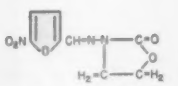
Effective against a wide range of bacteria found in urinary tract infections, including organisms resistant to other agents. It is indicated in pyelonephritis, cystitis and prostatitis, and there have been no reports of injury to kidneys, liver or blood-forming organs from its use.

TRICOFURON®

CONTAINS FUROXONE®

BRAND OF FURAZOLIDONE

for vaginal trichomoniasis



Tricofuron Vaginal Suppositories and Powder provide rapid relief of symptoms and a high cure rate in trichomonal vaginitis and secondary bacterial infections.

FURACIN®

BRAND OF NITROFURAZONE

topical antibacterial

After more than 10 years of clinical use, Furacin has now become the most widely employed single, topical antibacterial agent. It is available in appropriate dosage forms for prophylaxis or treatment of topical bacterial infections.

FURASPOR®

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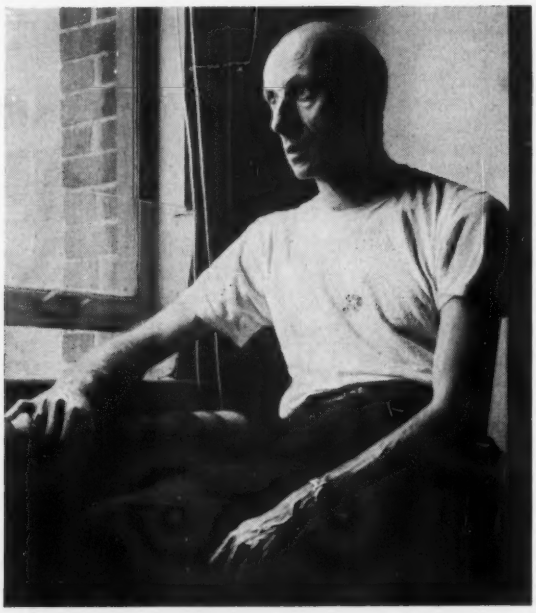
topical fungicide

Furaspor has broad antimycotic and antibacterial spectra.

*Dodd, M.C., and Stillman, W.B.: The in vitro bacteriostatic action of some simple furan derivatives, J. Pharm., Exp. Ther. 82: 11, 1944.

NITROFURANS

a significant new class of antimicrobials... products of Eaton research



Open the door to optimism for your palsied patient

COGENTIN

METHANESULFONATE (BENZTROPINE METHANESULFONATE)

Basic therapy includes COGENTIN—by far the most effective single agent for all types of parkinsonism. With COGENTIN the parkinsonian patient can be offered freedom from tremor and rigidity through judicious combination therapy. The powerful antispasmodic action of COGENTIN helps correct muscle spasm, frozen states and posture.[1]

"Benztropine [COGENTIN] was found to exert a highly selective action against certain symptoms of parkinsonism such as no other current drug affords.... Because of its safety and high efficacy and the absence of increased tolerance, its administration should be added to the treatment program of every patient with paralysis agitans...." [2]

1. J.A.M.A. 156:680, 1954. 2. J.A.M.A. 162:1031, 1956.

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THE NEUROLOGIC MANIFESTATIONS OF THE ACUTE LEUKEMIAS: A CLINICAL STUDY *

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INTRODUCTION

ALTHOUGH neurologic disorders are frequent in the acute leukemias, their clinical aspects generally have not been emphasized. Reports of nervous system manifestations in this disease have been published, but they have been either reviews of the literature [1, 2, 3, 4] or based upon retrospective studies.[3, 4] We have recently had an opportunity to observe the neurologic manifestations in a group of patients with acute leukemia. The purpose of the present communication is to direct attention to their frequency and course.

METHODS

This report comprises observations made on 63 patients with proved acute leukemia admitted to the National Cancer Institute between July 1, 1953, and April 30, 1956. Diagnosis in each instance was made by examination of a bone marrow specimen. Specific drugs used in the chemotherapy of acute leukemia included 6-mercaptopurine, 4-amino-N^{10}-methyl pteroylglutamic acid (methotrexate), and cortisone and related steroids. Individual therapeutic regimens will be discussed only where pertinent.

Whenever any suggestive evidence of a nervous system lesion developed, the patient was seen immediately in consultation by a staff member of the National Institute of Neurological Diseases and Blindness. Subsequently

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From the Medical Neurology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, and the Leukemia Section, General Medicine Branch, National Cancer Institute, National Institutes of Health.

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the patient was followed by members of the staffs of both the National Cancer Institute and the National Institute of Neurological Diseases and Blindness.

As the gross and microscopic anatomic alterations of the nervous system in leukemia have been described in detail previously,[5, 6, 7] neuropathologic findings will be reported only as they pertain to the clinical manifestations discussed.

Observations

The 63 patients observed are classified in table 1 by type of leukemia, age and sex. Forty-two of the 63 patients were dead and 21 were alive on April 30, 1956. Twenty-two of the 42 dead patients (52.4%) had 27 epi-

Table 1

Classification of 63 Patients with Acute Leukemia by Type, Age* and Sex

Type of Leukemia	No. of Patients	Sex	
		Male	Female
Granulocytic	23	14	9
Children	5	3	2
Adults	18	11	7
Lymphocytic	39	24	15
Children	24	19	5
Adults	15	5	10
Monocytic	1	1	0
Children	0	0	
Adults	1	1	
Total	63	39	24

* Patients less than 15 years of age at the time of admission to the Clinical Center are classified as children; patients past their fifteenth birthday are classified as adults.

sodes of nervous system disease under the authors' observation. Two patients who are still alive have each had one neurologic complication, making a total of 29 observed episodes.

The 42 dead patients are classified in table *2a* by type of leukemia, age and sex. The 22 patients who had neurologic symptoms prior to death are similarly classified in table *2b*. Neither the type of leukemia nor the age or sex of the patient appeared to influence the incidence of neurologic manifestations.

For purposes of discussion these episodes may be classified within three broad groups: (1) those due to complications of the disease (a-hemorrhage, b-infection); (2) those *presumed* to be due to leukemic infiltration (a-intracranial, b-peripheral nerve); (3) those due to miscellaneous disturbances. Fourteen episodes fall within the first group, 11 within the second, and four within the third.

(1a) The severest and most frequent nervous system manifestation of acute leukemia was intracranial hemorrhage. Thirteen episodes of intracranial bleeding occurred in 12 patients. Ten episodes appeared to be directly related to the death of patients. The first patient who survived such an episode later died of a second hemorrhage; the other two who survived an episode died subsequently of causes unrelated to intracranial bleeding.

In four of the 12 patients a generalized seizure heralded the onset of the bleeding. Other symptoms were fainting, vomiting, paresis, headache, and change in the mental state (slowing, drowsiness, somnolence, disorienta-

TABLE 2*a*

Classification of Dead Patients by Type of Leukemia, Age and Sex

Type of Leukemia	No. of Dead Patients	Sex	
		Male	Female
Granulocytic	17	11	6
Children	4	3	1
Adults	13	8	5
Lymphocytic	24	10	14
Children	10	6	4
Adults	14	4	10
Monocytic	1	1	0
Children	0	0	
Adults	1	1	
Total	42	22	20

TABLE 2*b*

Classification of Patients with Neurologic Symptoms Prior to Death

No. Patients with Neurologic Symptoms Prior to Death	Sex	
	Male	Female
10	7	3
3	2	1
7	5	2
12	4	8
4	2	2
8	2	6
0		
22	11	11

tion for time and place, coma). Although its onset was often precipitate, the first clinical manifestation in four patients was a moderate change in level of consciousness, which progressed within several hours or days to classic signs of intracranial hemorrhage. All patients who died due to intracranial hemorrhage had a platelet count below 25,000/mm.^{3} Of the three patients who survived an episode of intracranial hemorrhage, one had a platelet count of 82,500/mm.^{3}; another, 100,000/mm.^{3}; and the third (who died of a subsequent hemorrhage), 3,000/mm.^{3}

CASE REPORTS

A typical example of intracranial hemorrhage in a patient with acute leukemia is summarized:

Case 1. A 45 year old white male was admitted with a one-week history of symptoms of acute leukemia. Examination on admission revealed no evidence of nervous system disease. Hemoglobin was 10.3 gm./100 ml.; white blood cell count, 372,000/mm.^{3}, with 93% abnormal forms; platelets, 5,000/mm.^{3} A diagnosis of acute granulocytic leukemia was made. The following evening the patient briefly lost consciousness while in the bathroom and then lapsed into coma within a few minutes.

Examination revealed a comatose man with blurred optic disc margins and retinal hemorrhages, decreased random movements in the right arm and leg, and Babinski's sign bilaterally. Cerebrospinal fluid study revealed no cells. The coma gradually deepened, with loss of response to painful stimuli and dilatation of the pupils. Death occurred three hours after the beginning of the episode. At post mortem, cut sections of the brain revealed multiple hemorrhagic lesions to be present in the frontal, temporal and occipital lobes, the largest, over 5 cm. in diameter, being in the left temporal lobe.

(1b) Only one episode of nervous system infection occurred:

Case 2. A 25 year old male with acute granulocytic leukemia complained of headache and began to vomit. Neurologic examination revealed only nuchal rigidity. Hemoglobin was 6.6 gm./100 ml.; white blood cell count, 22,800/mm.^{3}, with 8% mature neutrophils. Spinal puncture showed an initial pressure of 200 mm. water. There were 3,800 white blood cells/mm.^{3}, with 92% mature neutrophils. Cerebrospinal fluid sugar was 29 mg.%; protein, 392 mg.%. Culture of the cerebrospinal fluid was positive for *Micrococcus pyogenes* var. *aureus,* coagulase-positive. The patient ran a gradual downhill course in spite of penicillin, tetracycline and erythromycin. He developed papilledema terminally and died 12 days after onset. Repeated spinal punctures prior to death showed pressure rising to 600 mm. water, white blood cells increasing to 7,700/mm.^{3}, sugar decreasing to 5 mg.%, protein increasing to 344 mg.%, and cultures constantly positive for *M. pyogenes* var. *aureus,* coagulase-positive.

Autopsy revealed thickening of the trabeculae of the arachnoid. Yellow thickening of the meninges was present, most marked within the thoracic cord. Minimal infiltration of leukocytes was seen in the subarachnoid tissue and space, and in the dura adjacent to the superior sagittal sinus. The spinal fluid culture remained positive for *M. pyogenes* var. *aureus,* coagulase-positive.

(2) Eleven episodes may be classified within the group presumed to be due to leukemic infiltration. Eight of these (a) clinically presented evidence of intracranial involvement, and three (b), evidence of peripheral nerve involvement.

(2a) All the episodes with intracranial involvement presented problems diagnostically, and some presented problems with respect to correlation of the clinical signs with the anatomic findings. All will be reported briefly.

Case 3. A 31 year old female with acute lymphocytic leukemia developed headache, lethargy, diplopia, decreased visual acuity, and proptosis of the left eye after antimetabolite therapy had been discontinued because of toxicity. Examination disclosed paresis of the left third cranial nerve, papilledema, and decreased central vision in the left eye. Skull films were negative. An electro-encephalogram showed a bilateral poorly organized background activity without focal abnormality. Spinal puncture revealed a white blood cell count of 115/mm.^{3}, 114 of which were abnormal

immature lymphocytes ("lymphoblasts").* The patient was begun on cortisone, 6-mercaptopurine and methotrexate. Regression of the neurologic symptoms and signs occurred concurrent with diminution in the size of liver, spleen and lymph nodes. Nevertheless, serial bone marrow aspirations indicated the persistence of many abnormal, immature lymphocytes.

A second episode occurred a few weeks later after therapy had again been discontinued because of toxicity to the antimetabolites. The patient once more developed headache and lethargy associated with the aforementioned neurologic signs. Similar antileukemic therapy brought about a neurologic remission, again without bone marrow improvement. The patient died later of non-neurologic causes, and no significant nervous system lesions were found at postmortem examination.

Case 4. A 47 year old male with acute granulocytic leukemia experienced dull, steady, suboccipital headache, which subsided when partial hematologic remission was induced with 6-mercaptopurine and methotrexate. Five months later, while on maintenance antimetabolite therapy, his headaches recurred, coincident with hematologic relapse. He gradually developed neck stiffness and disorientation to time and place. Neurologic examination revealed only nuchal rigidity and a right knee jerk more active than the left. Electro-encephalogram displayed a poorly regulated background activity and irregular, nonlateralized abnormalities. Initial lumbar puncture showed 27 white blood cells/mm.^{3}, 16 of which were myelocytes and myeloblasts. A second showed 90 white blood cells/mm.^{3}, with 89 abnormal forms. Cultures were negative. The patient had a partial hematologic remission and his symptoms abated, but within a few days the blastic crisis recurred and with it nuchal rigidity, disorientation and high fever. Spinal fluid now contained 211 white blood cells/mm.^{3}, all immature forms, with a protein of 23 mg.% and sugar of 108 mg.%. The patient died during this crisis. Postmortem examination revealed a smooth dura with a small, irregular zone of hemorrhagic staining on the under surface of the dura over the left lateral occipital region. No other significant central nervous system abnormalities were demonstrated.

Case 5. A one year old male with active acute granulocytic leukemia developed seizures, beginning in the right arm and spreading to the right side of the face and leg. Examination revealed a comatose patient with right hemiparesis and bilateral Babinski's sign. Roentgenograms demonstrated widening of all major cranial sutures. An electro-encephalogram showed diffuse slow waves, compatible with generalized brain involvement, constantly more pronounced on the left side.

Twenty-five days elapsed from the onset of this episode until death. Neurologic manifestations were at first characterized by right and left (mainly right) focal seizures, generalized seizures, bilateral Babinski's sign, right hemiparesis and transient anisocoria. Episodes of status epilepticus occurred during the first seven days. The patient then developed increased tone and flexion posture of the extremities, extension of the right leg occurring with the patient lying on his right side. During the first two weeks he received 453 r (in air) to two lateral ports on each side of the skull. Throughout the period he had varying degrees of nuchal rigidity and increased intracranial pressure. During the last seven days the abnormal posturing disappeared and he had no seizures. He remained unresponsive until death occurred due to systemic infection.

Spinal puncture at the onset of neurologic symptoms yielded slightly turbid fluid with 762 cells/mm.^{3}, all myelocytes and myeloblasts, protein of 372 mg.%, and sugar of 56 mg.%. Ventricular puncture five days later yielded fluid with a protein of 81 mg.%. No significant abnormalities in the shadows of the ventricular system were noted. Spinal fluid cultures were all negative.

* Differentiation between normal and abnormal forms within the spinal fluid may be quite difficult.

Postmortem examination showed pink subarachnoid fluid. The cerebral convolutions were moderately swollen; the sulci were narrowed. The left lateral sinus was thrombosed. These findings were not considered sufficient to explain his clinical manifestations in their entirety.

Case 6. A three year old male with active acute lymphocytic leukemia developed a limp in May, 1955. Significant findings on examination were a waddling gait and right facial weakness. Skull x-rays indicated separation of the coronal suture; an electro-encephalogram indicated a moderate degree of diffuse dysrhythmia, with a suggestion of the right hemisphere being maximally involved. A few days later the patient developed generalized hyperreflexia and bilateral Babinski's signs. Carotid arteriography showed no localized abnormality. Within a few weeks he developed papilledema and proximal muscle weakness. In the ensuing month, antileukemic therapy did not affect his hematologic status, although Babinski's signs, papilledema and right facial weakness regressed. On August 14, 1955, associated with *M. pyogenes* var. *aureus*, coagulase-positive septicemia, he had a generalized seizure. Neurologic examination revealed the right pupil to be larger than the left, the left knee jerk to be increased over the right, a bilateral ankle clonus and slightly blurred optic discs. Cerebrospinal fluid contained 160 red blood cells/mm.^{3}, 150 white blood cells/mm.^{3}, with 142 abnormal lymphocytes, and a protein of 10 mg.%. Spinal fluid cultures were negative. The patient became semicomatose and died the following day.

Postmortem examination disclosed the left frontal and parietal lobes to be partially overlaid by a thin subdural hemorrhage, 3 mm. in its greatest thickness. A recent subarachnoid hemorrhage was also found over the right middle frontal convolution. Extensive infiltration by leukemic lymphoid cells was seen in the piarachnoid over the brain and spinal cord. Perivascular accumulations of leukemic cells were noted around small capillaries and arterioles in the Virchow-Robin spaces. Sections of cervical, lumbar and cranial nerve roots revealed infiltration by leukemic cells. No infiltration of brain substance per se was noted.

Case 7. A four year old male with acute lymphocytic leukemia developed headache and, three weeks later, nonprojectile vomiting. Neurologic examination was significant only for the presence of papilledema. Spreading of all major cranial sutures was demonstrated by x-ray. His peripheral blood was entirely unremarkable, and a bone marrow aspiration revealed completely normal cellular elements. He was begun on 6-mercaptopurine and methotrexate despite apparent hematologic remission. Within three weeks his headaches and vomiting had subsided and the papilledema had decreased. In the ensuing six months the papilledema completely disappeared but he developed an insatiable appetite and gained 9.3 kg. Cranial sutures have remained separated. He has remained in hematologic remission.

Case 8. A two year old male with active acute lymphocytic leukemia developed earache and neck stiffness. Positive neurologic findings were limited to stiff neck and Kernig's sign. Widening of the major cranial sutures was noted on x-rays. Cerebrospinal fluid, with an initial pressure of 270 mm. water, contained 84 white blood cells/mm.^{3}, all lymphocytes. Protein was 20 mg.%; sugar, 41 mg.%; culture, negative. In the month following the onset of symptoms he had disappearance of neurologic signs, without change in the skull films, coincident with early hematologic remission.

Case 9. A 57 year old woman with active acute myelocytic leukemia developed dullness, lethargy and neck stiffness. The most striking clinical manifestations were tremulous movements of the face, head, palate and extremities, at a rate of three to four per second. This "tremulousness" occurred primarily in the antigravity muscles, particularly when the patient was maintaining posture. Clinically it resembled a

liver "flap," but no laboratory evidence of liver disease was found. Lumbar puncture showed no cerebrospinal fluid abnormalities.

The patient died the following day. At autopsy, diffuse leukemic infiltration of the cerebrum was found. Four centimeters behind each frontal pole, at the junction of the gray and white matter, there were focal lesions with the appearance of blood clots. In the left insula and in the left cerebral peduncle there were similar lesions which microscopically were red cell extravasations and leukemic infiltrates. A perivascular miliary leukemic infiltration was also present throughout the brain substance and in the left parietal dura.

(2b) Three patients presented signs and symptoms of peripheral nerve involvement. One patient exhibited signs of left mental nerve involvement. A second patient presented symptoms and signs of right fourth and fifth lumbar and first sacral nerve dysfunction, and another of left fifth lumbar and first sacral nerve disease. It was impossible to determine clinically whether the signs and symptoms observed in the latter two cases were due to nerve root or to peripheral nerve involvement. Since pathologic proof was inconclusive in all three cases, they will not be presented in detail.

(3) Four episodes may be classified in the miscellaneous group, since they do not clearly fall into any of the above. The first episode occurred in a 52 year old female with acute lymphocytic leukemia. She developed sharp pain along the left side of the nose and forehead and then fainted. Examination disclosed mild flattening of the left nasolabial fold, bilateral ankle clonus, and a Babinski's sign on the right. Spinal fluid examination and an electro-encephalogram were not remarkable. The clonus disappeared, though the right plantar response never returned completely to normal. Death resulted from a non-neurologic cause.

The second episode occurred in a 67 year old male with acute granulocytic leukemia who developed depression, paranoid tendencies, and misinterpretation of explanations. This was followed by depression of the state of consciousness and involuntary movements. Examination revealed intense icterus, generalized muscular rigidity broken by intermittent tremor, cogwheel phenomenon, intermittent choreiform movements, a Babinski's sign on the right, anisocoria but responsiveness to light and accommodation, and disorientation as to time and place. As there were markedly abnormal liver function tests and an elevated blood ammonia level, the clinical impression was that his central nervous system disease was a manifestation of liver failure. The patient lapsed into deep coma before death.

Lastly, two episodes of psychosis are placed within this group. One of these appeared to be directly related to therapy with cortisone; another appeared when the patient was admitted to the hospital and disappeared after discharge.

Discussion

In the largest previous review of the neurologic manifestations in patients with acute leukemia, Schwab and Weiss [3] found that 27 of 120 patients

(22.5%) had neurologic symptoms or signs. Brandt [4] found neurologic manifestations in 18 of 206 patients (8.6%) with both acute and chronic leukemias. In a group of 31 patients with acute and chronic leukemia, Leidler and Russell [6] found clinical neurologic complications in 11 (35.5%). Nordlander [8] reported clinical neurologic manifestations in 27 of 154 patients (17.5%) with both acute and chronic types. Even when the four patients placed within the "miscellaneous" disorder group are excluded, 42.9% of our patients had nervous system complications. This difference may be explained by the fact that the frequency of nervous system complications in our series was obtained after specific study of patients during the course of their illness, whereas that of others was based on hospital records. On the basis of their review of the pathologic findings, Schwab and Weiss [3] suggested that "from 25 to 50% of all cases of leukemia should exhibit some clinical sign of neurologic involvement."

As in other series,[3, 6, 8] there was no significant difference in the incidence of neurologic complications in the different types of acute leukemia. Our data further suggest that there is no significant sex or age difference, though Leidler and Russell [6] found the neurologic complications to be twice as frequent in males as in females.

As stated, intracranial hemorrhage is a frequent and severe complication. It was the direct cause of death in 10 of 42 patients, and appeared related to the bleeding tendency so common in this disease. The diagnosis of such bleeding may be more difficult, since retinal hemorrhages, ordinarily a valuable sign of intracranial bleeding, are frequently present in leukemic patients without concomitant intracranial complications. In this instance, a subhyaloid hemorrhage confirms the presence of intracranial bleeding. Two of our patients displayed this sign. Diagnosis may also be difficult when the onset is heralded by gradual mental changes (as occurred in four of our patients).

Only one patient developed an infection of the central nervous system, a rather low figure considering the frequency of infections in patients with acute leukemia. Nevertheless, there is the ever-present problem of differential diagnosis between bacterial meningitis and central nervous system disease due to leukemic infiltration itself. When an afebrile patient has developed symptoms and signs of meningismus and remained afebrile, we have had less hesitation in invoking leukemia per se as the explanation. In febrile patients, only negative spinal fluid cultures rule out the presence of a bacterial meningitis. Although very high protein and low sugar suggest bacterial infection, similar findings [3, 9] have been noted in "leukemic meningitis." The absence of mature neutrophils in suspected pyogenic meningitis in no way contraindicates the diagnosis, for the polymorphonuclear response to infection in leukemia, as Jaffé [10] originally indicated, depends upon the extent of the functional reserve of the marrow. Thus, although we have not seen such a case, theoretically pyogenic meningitis might occur in acute leukemia without a granulocytic response in the cerebrospinal fluid.

Of particular interest in the group presumed to be due to intracranial leukemic infiltration is the fact that five of seven patients improved from a neurologic standpoint with antileukemic therapy. In two patients (cases 3 and 6), neurologic improvement was not accompanied by any measurable change in the hematologic status of the patient. This suggests that, in certain instances, antileukemic therapy may be effective against the central nervous manifestations of acute leukemia, though it remains ineffective in inducing a bone marrow remission.

On the other hand, neurologic abnormalities may become manifest in the presence of peripheral blood and bone marrow remission of the disease (as occurred in case 7),* and antileukemic therapy may be effective in bringing about neurologic improvement in such an instance. This patient is remarkably similar to two patients with acute leukemia reported by Sansone.[9] His patients developed similar signs and symptoms, including obesity, also while in hematologic remission. He reported transient improvement in the neurologic aspect of the disease after intrathecal aminopterin. Autopsy in one of his patients revealed meningeal leukemic infiltration and a parenchymal leukemic infiltration almost exclusively localized in the diencephalohypophysial region. The latter finding was invoked as a cause of the obesity.

Widening of the cranial sutures occurred in four children in this group. On the basis of clinical symptoms and signs, it had been our feeling that cranial suture widening was a direct consequence of increased intracranial pressure. However, in a recent report [11] such separation has been ascribed to leukemic infiltration in the connective tissue between the sutures of the skull. In one autopsied patient, Hitzig and Siebermann believed that the degree of infiltration was sufficient to account for the separation seen. In this 40 month old child the cerebrospinal fluid dynamics and cytology were apparently normal. In their second case, a 45 month old child, a lumbar puncture yielded 928 cells (875 lymphocytes, 53 segmented forms). Since there was a history of exposure to mumps and a mumps complement fixation titer of 1:128, the authors felt that this might well represent an episode of mumps meningitis. The complement fixation titer was not followed serially. Regression of signs of meningeal irritation in this patient coincided with bone marrow remission. There was no postmortem examination. In many respects this last case closely resembles ours.

In the group with presumed leukemic infiltration, autopsies were performed in five patients who have died. In only two (cases 6 and 9) were the central nervous system findings considered to be sufficient to account for the clinical manifestations. Similar lack of clinicopathologic correlation in these instances has been noted previously.[6, 8]

Manifestations of peripheral nerve or nerve root disease in patients with leukemia have previously been recorded.[12] In some patients no infiltrations

* We have recently observed another patient with acute leukemia who developed similar central nervous system abnormalities in the presence of complete bone marrow remission.

were found at autopsy to explain the symptoms (a situation which occurred in our three cases). Even where nerve root infiltrations are found, the clinical signs often are out of proportion to the anatomic lesions.

In acute leukemia, as in any other fulminating illness, nervous system manifestations may occur as a result of drug therapy, secondary metabolic alterations, or the patient's reaction to the illness. Three of four patients in the "miscellaneous" group had such manifestations.

Summary

1. Sixty-three patients with acute leukemia were studied for the presence of neurologic manifestations.

2. Neurologic manifestations occurred in 22 of 42 patients who were followed until their deaths.

3. The nature and course of these manifestations are discussed.

4. Neurologic manifestations may improve with antileukemic therapy even in the absence of bone marrow evidence of improvement.

5. Neurologic manifestations may occur in the presence of bone marrow remission.

Acknowledgment

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Summario in Interlingua

Ben que disordines neurologic es frequente in le acute leucemias, lor manifestationes pathologic plus tosto que lor aspectos clinic es generalmente sublineate in le litteratura. Le presente reporto consiste de observationes clinic in 63 patientes con provate acute leucemia, studiate al Instituto National de Cancere. Quaranta-duo de illes esseva morte al tempore del redaction de iste manuscripto. Vinti-duo de ille 42 patientes (52,4 pro cento) habeva 27 episodios de morbo de systema nervose sub le observation del autores. Ni le typo de acute leucemia ni le etate o le sexo del patiente pareva influentiar le incidentia de manifestationes neurologic.

Iste episodios es classificate in tres gruppos: (1) Illos debite a complicationes del morbo (a- hemorrhagia, b- infection); (2) illos *presumptemente* debite a infiltrationes leucemic (a- intracranial, b- peripheric); e (3) illos debite a disturbationes miscellanee.

Dece-tres episodios de sanguination intracranial occurreva in 12 patientes. Dece de iste episodios esseva apparentemente implicate in le morte del patientes. Le hemorrhagias intracranial pareva esser le consequentia del tendentia sanguinatori que es si commun in iste morbo. In multe casos le diagnose de tal hemorrhagias es difficile, proque sanguination retinal—que es ordinarimente un indicio significative de hemorrhagias intracranial—occurre frequentemente in patientes leucemic sin concomitante complicationes intracranial. In iste situation, un hemorrhagia subhyaloide confirma le presentia de sanguination intracranial. Occurreva solmente un episodio de infection del systema nervose. Il se tractava in iste caso de meningitis causate per *Micrococcus pyogenes* var. *aureus*, con positivitate a coagulase.

Dece-un episodios formava le gruppo presumptemente debite a infiltration leucemic. In octo il habeva signos de implication intracranial e in tres periphero-nervose. Un facto de interesse special es que cinque del septe patientes representate in iste gruppo se meliorava ab le puncto de vista neurologic sub le influentia del therapia anti-

leucemic. In duo patientes un melioration neurologic occurreva sin mesurabile alterationes parallel in le stato hematologic. Isto pare indicar que in certe casos un therapia antileucemic pote esser efficace contra le manifestationes del morbo in le systema nervose central ben que illo remane inefficace in inducer un remission in le medulla ossee. Del altere latere, anormalitates neurologic pote manifestar se in le presentia de remission del morbo in sanguine peripheric e medulla ossee, e etiam in tal casos il es possibile que le therapia antileucemic se prova capace a effectuar un melioration neurologic. In iste gruppo, le constatationes pathologic non sufficeva a explicar le observationes clinic in omne casos autopsiate. Le mesme observation ha essite reportate per plure previe autores.

Quatro episodios esseva classificate in le gruppo miscellanee (un caso de inexplicate dolores facial e perdita de conscientia, un caso de coma hepatic, e duo casos de psychosis).

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ANTICOAGULANT THERAPY: ELIMINATION OF SOME COMMONLY OCCURRING PITFALLS *

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The theoretic possibility of controlling thrombo-embolic disease with agents that inhibit blood clotting is well recognized. There is no question that undesirable thrombotic complications can be prevented when anticoagulant agents are properly utilized. However, the dangers resulting from this type of treatment appear in the literature [1] all too frequently. Dicumarol has earned the reputation of being one of the most dangerous drugs in common use.[2] This is indeed unfortunate, because this drug can be administered safely and effectively.

One of the first essentials to successful anticoagulant therapy is *proper* laboratory control. There are very few situations in clinical medicine where the physician is so dependent upon the laboratory. Unfortunately, not all of the prothrombin tests in common use today can be considered adequate. This is, perhaps, best emphasized by the following statement, quoted from an article [2] summarizing 11 fatalities reported to have occurred from 1946 to 1951: "Regardless of the short- or long-term use of this anticoagulant, and despite adequate laboratory control, nine other fatalities occurred."

During the last seven years, extensive experience with a new prothrombin test has been accumulated. A procedure for combined anticoagulant therapy with heparin and Dicumarol has been devised which is simple, safe and effective. It is the purpose of this communication to describe the details and rationale of this program. There will be no consideration of the indications or contraindications for anticoagulant therapy.

In 1949 the Quick prothrombin test [3] was in use at the Los Angeles County Hospital in the routine laboratory. Frequent complaints of inaccuracy and unpredictability were registered by the staff members. Numerous hemorrhagic episodes had occurred which, for lack of a better reason, were blamed directly or indirectly on the laboratory. A critical examination of the prothrombin test was undertaken and it was concluded that the procedure was unsatisfactory. It was simple to perform but so difficult to standardize that accuracy and sensitivity were, by necessity, sacrificed. Furthermore, errors introduced from instability of blood specimens made the test merely a rough estimate of prothrombin activity. For use with a drug as potent

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as Dicumarol, this created a difficult situation. However, little could be done from the laboratory standpoint because no other simple methods were available which offered much in the way of improvement.

Early in 1950 the report of Dr. Paul Owren [4] from the University of Oslo came to our attention, and with this as a starting point a prothrombin test was evolved which appeared to satisfy our requirements.[5] The procedure was technically somewhat more complicated, but ease of standardization more than compensated for this. Reproducible results were guaranteed by the use of a stable, dried prothrombin reference standard. Variations in levels of clotting factors were controlled; these are critical in the Quick test and may give rise to serious errors. Sensitivity was increased manyfold. A technic of preservation of prothrombin activity in drawn blood was developed [5] which satisfied our requirements, and which is now being used by Dr. Owren to preserve specimens in the mails.[6]

Since the introduction of the modified Owren * procedure at the Los Angeles County Hospital in 1950, more than 5,000 patients have been treated with anticoagulants. The interns and residents have administered all drugs without the direct supervision of an anticoagulant team since 1951. The results are outstanding because the incidence of bleeding has been exceptionally low and there have been no deaths which could be directly attributed to anticoagulants. A controlled study involving more than 600 patients with congestive heart failure was carried out during this period.[7] The incidence of bleeding in treated patients was 2.8%, only 0.1% higher than that in the control group. The incidence of unsatisfactory results, which included deaths and nonfatal thrombo-embolic episodes, dropped significantly from 31% in the control group to 10% in those receiving anticoagulants. From all indications, effective therapy had been provided without increasing the risk of hemorrhage. Reports from Owren's clinic in Oslo reveal similar results.[8, 9]

Once a decision has been reached to use anticoagulants, it is our policy to institute therapy with heparin. This agent is the most efficient of the available anticoagulants. It has an immediate effect on the clotting mechanisms, acting in two different manners: first, by inhibiting thrombin formation; second, by enhancing the destruction of preformed thrombin. The latter may be extremely important in preventing the propagation of clots which have already formed. Quick has postulated that thrombin is extruded from the interstices of fibrin clots during syneresis or retraction, thus acting as a stimulus for further clot formation.[10] Such a cycle of thrombus propagation is readily prevented by heparin, an advantage not shared by Dicumarol. However, this advantage is offset somewhat by the expense of heparin and the necessity for parenteral administration.

The anticoagulant potency of heparin is of such magnitude that 10 mg. (1,000 units) will render 1 L. of normal blood almost completely incoagu-

* Reagents for this procedure were furnished by Hyland Laboratories, 4501 Colorado Blvd., Los Angeles, California.

lable; as little as 1.5 mg. will usually produce a measurable effect.[11] The dosage schedule we recommend is an initial intravenous injection of 50 mg. This is followed within four hours by a deep subcutaneous injection of 100 mg. of concentrated heparin (200 mg./c.c.). We continue this dosage every eight hours until therapeutic hypoprothrombinemia can be produced with one of the prothrombin depressing agents. During this period it is felt that little can be gained from the use of clotting times. The indicated dosage schedule provides an adequate anticoagulant effect in most patients, with minimal risk of hemorrhage.

The concentrated heparin solutions are preferred to those which employ a material which retards absorption. The anticoagulant effect is more predictable, there are fewer complications at the site of injection, and, if therapy must be terminated, the heparin effect wears off rapidly. In the rare event that the effect of heparin must be reversed immediately, this may be accomplished simply by the intravenous injection of protamine. The action of protamine is rapid and lasts only a few hours.[12] The dose to be used can be predicted from clotting times determined in glass tubes by the usual technic. Fifty milligrams are usually sufficient. However, if the clotting time does not return to normal, another 50 mg. may be indicated. Excessive amounts of protamine are contraindicated because these may produce an anticoagulant effect.[13]

On rare occasions there may be a need for more heparin than that indicated in the above dosage schedule. This may happen during the acute stages of thrombophlebitis or following extensive trauma.[14] In these circumstances it may be necessary to increase the subcutaneous dose of heparin to 150 mg. The frequency of administration usually need not be increased. This dosage schedule should not be adopted unless clotting times are checked. If the clotting time is not prolonged more than three times normal in two to three hours after injection of heparin, the increased dosage may be indicated.

Once treatment has been instituted with heparin, the next problem concerns the choice of a drug to depress the synthesis of prothrombin. Dicumarol, which has been used the most, has the disadvantage of unpredictability of response, which is probably due to variable absorption from the gastrointestinal tract. For this reason it is desirable to hold another drug in reserve should difficulties be encountered. Tromexan and Cumopyran do not offer many advantages. The phenylindandione derivatives appear to be more easily controlled, but occasional agranulocytosis [15] has been reported with this agent. The most recently developed of the coumarin anticoagulants is Warfarin, or Coumadin.[16] It offers sufficient advantages so that it may well become the anticoagulant of choice. The principal reason for this lies in its water solubility, which leads to more predictable absorption from the gastrointestinal tract. It can also be given intravenously, which may be an advantage in certain patients in shock or in congestive failure, where edema of the gut wall may interfere with absorption. The maintenance dose

appears to be more reproducible from day to day than is that of Dicumarol.

With these agents it is our aim to depress the prothrombin level to somewhere between 10 and 30% of normal. With the use of the modified Owren prothrombin test, this can be accomplished safely even while the patient is receiving heparin. Extensive use of combined therapy with this prothrombin test has shown that therapeutically administered heparin does not interfere technically or produce an additional bleeding hazard. *Dilution of plasma in the Owren test eliminates the technical interference of heparin, which is unavoidable with the Quick test or any of its modifications using whole plasma.*

The induction of hypoprothrombinemia requires relatively large priming doses of drug. We suggest an initial dose of Dicumarol of 200 mg. for the small individual, 250 mg. for the average, and 300 mg. for the large. Coumadin is approximately four times as potent as Dicumarol, so that a priming dose of 50 to 75 mg., oral or intravenous, may be used. Subsequent doses are determined from the response of the prothrombin level and cannot be predicted by a "rule of thumb" basis. The Owren test offers approximately a tenfold increase in sensitivity over the Quick, so that prothrombin levels may be followed progressively down to the therapeutic range, decreasing the dosage accordingly. A common mistake is to depress the prothrombin to a dangerously low level during this stage. The prothrombin tests employing whole plasma are so insensitive that response to the priming doses often is not apparent until it is too late.

Once an adequate depression of the prothrombin level is obtained, it is important to realize that small changes in dosage will usually produce a significant response in prothrombin level. It is preferable to maintain the patient on a constant daily dose. For instance, the daily administration of 37.5 mg. of Dicumarol is preferable to intermittent doses of 25 and 50 mg. Occasionally, even finer dosage adjustment will be necessary, and in this event a suspension of Dicumarol in water may be prepared so that one teaspoonful will contain 10 mg.

A problem also arises if the prothrombin level falls below 10%. We no longer fear this occurrence, but merely discontinue the administration of drug. Often the prothrombin will remain depressed for several days, and when it does start to rise it almost invariably rises above the therapeutic range, even though therapy is promptly re-instituted. To prevent this sudden rise, therapy should be re-instituted with small doses as the 10% level is approached. For this reason we now recommend the routine reporting of prothrombin to levels as low as 5%.

An occasional emergency may arise which necessitates rapid correction of the hypoprothrombinemia. Intravenous injection of emulsified vitamin K_1 (Mephyton) produces a rapid rise in prothrombin which may usually be detected in a few hours.[17] The prothrombin level may be expected to rise above normal in 12 to 36 hours and to remain there for several days. Fifty

milligrams of vitamin K_1 are a suitable dose, and may be repeated if the prothrombin level does not rise at the expected rate.

The desirable therapeutic level with the modified Owren test appears to be between 10 and 30% of normal. Our control studies indicate that the incidence of bleeding is not increased significantly as long as the prothrombin is kept above 10%.[7] An appreciable decrease in thrombotic episodes was noted as long as the prothrombin level was kept consistently below 60%. Depression of prothrombin to the lower levels provided maximal protection. Smith has recently presented evidence that prothrombin levels of 10 to 20% with the modified Owren test are equivalent to 30 to 50% by Quick's method.[18] Accordingly, he has raised his therapeutic range and reports a significant reduction in hemorrhage. There is no question that the modified Owren method gives lower answers in the therapeutic range. It should be emphasized, however, that this test reveals the correct level of prothrombin activity. The Quick method gives falsely high answers in the lower ranges because of errors produced by standardization with saline-diluted plasma. When the reference plasma is properly diluted, using prothrombin-free plasma as described by Stefanini,[19] the discrepancy is readily apparent.

Comparisons between the Quick and the modified Owren tests are inconsistent because of another variable produced when the blood is allowed to stand. Contrary to general opinion, the prothrombin time tends to become faster during the first few hours after the blood is drawn.[20, 21] This change, which often occurs rapidly, is prevented in our modification of the Owren test by using an oxalate anticoagulant containing a trace of heparin, which stabilizes prothrombin activity. Thus, the degree of difference between the two tests is also affected by the amount of time the specimen stands before the Quick test is performed.

We have obtained excellent results over an extended period with the modified Owren test using the therapeutic range indicated. We are convinced that the incidence of hemorrhage has been negligible during this period primarily because of the use of this prothrombin method. In some institutions it has been possible to obtain comparable results by using a team of specialists who administer and supervise all therapy. In our hospital the interns and residents administer all of the anticoagulants. It therefore seems reasonable to assume that, given adequate laboratory facilities, the beneficial results of anticoagulant therapy can readily be made available to patients outside of research centers and large hospitals.

Summary

Anticoagulants have been administered to more than 5,000 patients during the last five years. Prothrombin levels have been determined exclusively by a modification of Owren's method, using a dried reference standard and a special anticoagulant for preservation of prothrombin activity. The inci-

dence of bleeding only slightly exceeded that to be expected in untreated patients. There have been no deaths attributed to anticoagulants.

The presentation concerns rationale of anticoagulant selection, recommended technics of therapeutic management, and critical analysis of laboratory methods for measurement of prothrombin.

SUMMARIO IN INTERLINGUA

Le necessitate del instruction in le uso de drogas anticoagulante es illuminate per le facto que in 1951 un plus grande numero de mortes esseva reportate como resultato del uso de Dicumarol que como resultato de non importa qual altere agente therapeutic. Inter 11 mortes reportate, nove concerneva patientes qui habeva recipite un "adequate" controlo laboratorial. Isto es deplorabile, proque il es possibile administrar le droga simple- e securmente.

In le curso del passate cinque annos, anticoagulantes esseva administrate al Hospital del Contato de Los Angeles a plus que 5000 patientes. In le majoritate del casos le tractamento esseva sub le direction de medicos in residentia e de internos del hospital. Como regula general le tractamento esseva un combination de therapia a heparina e a Dicumarol. Le nivellos de prothrombina esseva determinate exclusivemente per un modification del methodo de Owren in que esseva usate un siccate standard de referentia e un anticoagulante special pro le preservation del activitate de prothrombina. Le incidentia de sanguination esseva minimal. Illo excedeva per solmente leve grados illo expectate in patientes sin tractamento anticoagulante. Occurreva nulle mortes que esseva attribuibile unicamente al uso de coagulantes.

Le uso del modificate test prothrombinic de Owren offere un numero de avantages practic que justifica su uso. Le plus importante de iste avantages es le exactitude e le reproducibilitate del methodo. In plus, le methodo offere inusual grados de stabilitate del specimens de sanguine e meliorate nivellos de sensibilitate, e illo facilita le uso de un therapia combinate con heparina. Heparina administrate in le usual doses therapeutic non obstrue iste forma del test de prothrombina.

Le presente articulo concerne le rationamento del selection de anticoagulantes, le technicas recommendate in le regime therapeutic, e le analyse critic de methodos laboratorial pro le mesuration de prothrombina. Le articulo non se occupa del selection de patientes pro therapias a anticoagulante.

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CORTISONE–THYROID THERAPY OF METASTATIC MAMMARY CANCER *

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INTRODUCTION

Recent studies by the New York State Department of Health indicate that, in that area, mammary cancer is the most frequently reported of all human tumors and is the most important single cause of death from cancer.[1] As a result of the magnitude of this public health problem and the well known rôle of sex hormones in mammary development, there has been much interest recently in hormonal treatment of inoperable mammary cancer. It has been shown that various androgens and estrogens frequently induce subjective and objective remission of the disease,[2] and that oophorectomy,[3] total adrenalectomy [4] and total hypophysectomy [5] may likewise temporarily ameliorate the signs and symptoms of metastatic cancer in selected patients. There is increasing acceptance of the concept that cancers responding to endocrine treatment are those which remain partially dependent upon endogenous sex hormones for continued proliferation. All the effective therapeutic measures developed thus far induce extensive alterations of endocrine balance as a result of the interlocking activities of the adenohypophysis with the gonads, adrenal cortex and thyroid gland.

The temporary nature of the remission of breast cancer induced by sex hormone therapy is well known, but there is less appreciation in practice of the hazards of stimulation of neoplastic growth by estrogens administered to premenopausal or menopausal patients,[6] and of the possibilities of androgenic stimulation of the tumor.[7] The present study was undertaken three years ago to evaluate the use of cortisone and cortisol (hydrocortisone) as palliative measures replacing other types of hormone therapy, and to see whether these compounds, necessary for maintenance therapy of totally adrenalectomized or hypophysectomized patients, have of themselves any inhibitory effects upon breast cancer. This report presents clinical, pathologic and biochemical observations of 30 unselected patients receiving cortisone or cortisol for periods of from 10 days to over 37 months for treatment of metastatic mammary carcinomas shown by biopsy or unequivocal radiologic signs.

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From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine. These studies have been assisted by teaching and research grants from the United States Public Health Service and an Institutional Grant from the American Cancer Society. Merck, Inc. generously provided part of the steroids utilized.

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Endocrine Pathology of Mammary Cancer

Successful use of cortisone in the treatment of mammary cancer must be accompanied by an understanding of the major areas of endocrine disturbance in this disease. Multiple pathologic changes have been noted in the ovaries, thyroid, adrenal or hypophysis of nearly all of a large series of autopsied patients with cancer of the breast, in contrast to a control series of patients dying of non-neoplastic disorders, of whom less than one-half had endocrine abnormalities.[8, 9] Cortical ovarian stromal hyperplasia has been most frequently noted—80 to 85% of patients, as compared to 37% of controls—and appears to be correlated to some extent with a relatively good prognosis.[10] Ovarian cortical stromal hyperplasia occurs with increasing frequency in the older age groups during and after menopause, and may account in part for the continued excretion of estrogens which several observers have noted in postmenopausal patients with breast cancer.[11, 12] There is recent evidence that the postmenopausal ovary can synthesize estrogens from radioactive acetate in vitro.[13]

Both ovary and adrenal cortex have been implicated as sources of estrogen production. The only reliable method of eliminating ovarian estrogen (and androgen) production is surgical castration,[12] although sex hormone production by the adrenal cortex can be reduced by cortisone or cortisol therapy.[12, 14-17] The clinical effectiveness of cortisone in inhibiting the production of adrenocortical sex hormone was first shown by Wilkins in 1950 in suppression of the virilizing manifestations resulting from adrenocortical hyperplasia in females, and it is believed to result from inhibition of ACTH secretion by the exogenous corticoid.[14-16] Cortisone therapy has repeatedly been shown to induce involutional changes in the adrenal cortex,[18] but it does not impair ovarian structure or function.[16] Secretion of follicle-stimulating hormone is augmented by cortisone therapy.[19, 20] Therefore, palliation of sex hormone-dependent mammary cancer by cortisone might be anticipated on the basis of clinical and experimental observations, as a result of inhibition of the adrenal cortex, only in the total absence of ovarian function. As a result of our early experience we now routinely subject to oophorectomy all patients under 65 with metastatic breast cancer prior to cortisone therapy, but after this age, prolonged remissions have been obtained with cortisone administration alone. Several previous negative reports on the value of cortisone in cancer of the breast have neglected these physiologic considerations,[20-22] although others have noted cortisone-induced remissions when surgical castration was included in the therapeutic preparation of the patient.[23-26]

Dosage Factors in Cortisone Therapy

Dosage of cortisone is of crucial significance in the treatment of breast cancer if the objective is to reduce production of endogenous sex hormone

to a minimum. Cortisone and cortisol are not directly converted to estrogenic substances.[27, 28] Their major pathway of metabolism occurs via reduction to tetrahydrocortisone or tetrahydrocortisol, which is then excreted. If the side chain at C17 is lost prior to excretion, the excreted metabolites consist chiefly of biologically inactive etiocholane isomers. About 10% of the administered steroid (which loses its side chain at C17) is converted to androgenic 17-ketosteroid compounds, such as 11-beta-hydroxyandrosterone and 11-keto-androsterone.[27] With maintenance doses in excess of 100 mg. of cortisone daily, a significant increase results in urinary androgens and 17-ketosteroids.[29] These androgens are potentially convertible to estrogens, especially in the ovary, where conversion of testosterone to estradiol-17B has recently been noted.[30] Administration of excessive amounts of cortisone (200 to 400 mg./day) for long periods not only produces all the side-effects of hypercortisonism, but also perhaps inhibits some of the defense mechanisms against cancer which involve fibroplasia.[31] Wilkins concluded that the minimal effective oral dose of cortisone for inhibition of adrenal hyperplasia was 25 to 75 mg. daily, evenly distributed throughout the 24 hours.[14–16] Therefore, we have usually maintained our patients on divided doses totaling 50 to 100 mg. per day, after initial doses of 200 to 300 mg. daily for one or two days.

Small doses of desiccated thyroid (15 to 120 mg./day) have been given to most patients, usually after from four to eight weeks of cortisone therapy, on empiric grounds, to provide additional inhibition of the hypophysis and prevent latent myxedema. Cortisone therapy may precipitate manifestations of myxedema in some hypothyroid patients, and it is known to inhibit radioiodine uptake by the thyroid.[32] Observations of patients with anterior hypophyseal deficiency also indicate an interdependence of thyroid hormone and adrenocortical hormones in the maintenance of an optimal endocrine balance.[33]

Additional therapy given to some patients has included vitamin D, vitamin B_{12}, calcium lactate and sedatives. Opiates have seldom been necessary. In only four patients was ionizing radiation or medication given during the first two or three months therapy with cortisone and thyroid.

Criteria of Remission

Subjective evidences of remission in patients receiving cortisone are open to doubt because of its alleged property of inducing euphoria, which heretofore seems to have escaped objective demonstration in double-blind controlled studies. There is no evidence that cortisone therapy alters pain-threshold measurements.[34] We have therefore not included subjective criteria of remission although improved appetite, capacity for physical activity, and relief of pain have accompanied objective improvement in all instances.

Hot flashes have been carefully tabulated as evidence of estrogen withdrawal, since they have been correlated with the release of excessive quan-

TABLE 1

Patients Receiving Cortisone or Hydrocortisone for Metastatic Cancer of the Breast

Pt.	Sex	Age	Date	Operation	Pathology	Date of Recurrence	Principal Metastases	Pathology
H. M.	F	65	Dec. 1952	Rad. mast.	Cancer	Oct. 1953	Shoulder girdle, L1	—
L. G.	F	34	Dec. 1952	Rad. mast.	Adenoca.	Dec. 1952	Skin, spine, liver	Met. ca. (autopsy)
M. S.	F	70	May 1948	Rad. mast.	Poorly diff. ca.	Aug. 1952	Diffuse bone, skin	—
H. B.	F	65	Apr. 1951	Rad. mast.	Anaplastic duct cell type	Apr. 1953	Skin, lymph nodes, bone	Met. ca. (autopsy)
C. C.	F	64		None	—	Apr. 1950	Diffuse bone	Met. ca. (autopsy)
E. H.	F	53	Sept. 1951	Rad. mast.	Cancer	Jan. 1953	Diffuse bone, skin	Met. ca. (biopsy)
C. M.	F	75	Apr. 1948	Rad. mast.	Poorly diff. ca.	May 1949	Diffuse bone, skin	Met. ca. (biopsy)
C. T.	F	34	Jan. 1954	Rad. mast.	Cancer	July 1954	Spine, liver	—
M. C.	F	40	Feb. 1950	Rad. mast.	Undiff. ca.	Feb. 1954	Lung, lymph nodes, skin	Met. ca. (biopsy)
E. Co.	F	64	Nov. 1948	Rad. mast.	Poorly diff. ca.	1953	Lymph nodes, bone, lung, liver	Met. ca. (autopsy)
A. S.	F	49	Feb. 1953	Rad. mast.	Cancer	Jan. 1954	Liver	—
H. C.	F	53		None	—	June 1952	Liver, bone, skin	Met. ca. (autopsy)
E. Ca.	F	59	1951	Rad. mast.	Scirrhus ca.	Apr. 1953	Lung, bone, eye	—
M. N.	F	47	Mar. 1951	Rad. mast.	Cancer	Sept. 1951	Spine	Met. ca. (autopsy)
R. H.	F	42	1951	Rad. mast.	Cancer	Apr. 1955	Lung and pleura, liver, breast	Met. ca. (inflamm.)
M. Mc.	F	28	Jan. 1954	Bilateral Rad. mast.	Scirrhus ca.; undiff. ca.	May 1955	Spine, liver	Met. ca. (autopsy)
W. K.	M	57	1948	Rad. mast.	Adenoca.	Sept. 1950	Lung, sternum	—
M. M.	F	58	1952	Rad. mast.	Cancer	Jan. 1954	Diffuse bone	—
D. C.	F	68	1942	Rad. mast.	Cancer	1952	Lymph nodes, mediastinum	—
A. W.	F	53	1948	Rad. mast.	Cancer	1953	Lymph nodes, cerebellum, skull	Met. ca. (autopsy)
F. L.	F	43	Jan. 1955	Rad. mast.	Undiff. ca. (inflamm.)	Mar. 1955	Lymph nodes, skin	Met. ca. (autopsy)
A. P.	F	48	1946	Rad. mast.	Cancer	1948	Breast, lung, bone	—
K. P.	F	43	1949	Rad. mast.	Cancer	1950	Lung, bone	—
M. B.	F	71	1944	Rad. mast.	Cancer	1952	Shoulder girdle, humerus	Met. ca. (operation)
M. P.	F	47	1952	Rad. mast.	Cancer	1953	Lung, brain	—
J. R.	F	49	Jan. 1954	Rad. mast.	Cancer	Sept. 1954	Lung	Met. ca. (autopsy)
E. M.	F	44	Jan. 1954	Rad. mast.	Cancer	Feb. 1955	Lung, bone	Met. ca. (autopsy)
L. B.	F	48	Feb. 1954	Biopsy	Mucinous adenoca.	Feb. 1954	Both breasts, lung	—
J. L.	F	59	June 1950	Rad. mast.	Poorly diff. ca.	June 1952	Lymph nodes, lung, brain	
S. M.	F	84	Mar. 1955	Biopsy	Undiff. ca.		No metastases proved	

tities of pituitary gonadotropins by Nathanson and co-workers.[35] Excretion of pituitary follicle-stimulating hormone has been serially estimated in the study, using the immature mouse uterus assay procedure,[36] in order to confirm objectively any augmentation of anterior pituitary activity resulting from changes in the level of circulating sex hormones.

Objective manifestations of improved condition included in this study have been: (1) gain in body weight, free of any evidence of edema; (2) return to normal daily physical activity, including previous occupation; (3) survival in ambulatory status; (4) marked decrease in urinary calcium ex-

TABLE 2

Extent of Metastases and Physical Activity when Treatment Was Initiated

	Fully Ambulatory	Partially Ambulatory	Largely Bedridden
Local disease only: breast, regional lymph nodes, or one area of osseous disease	M. B. S. M.		
Extensive parietal soft tissue metastases, with minimal osseous disease	H. B.* D. C.* F. L.		
Extensive osseous metastases, with minimal parietal soft tissue disease	L. G.* C. C.* C. M.* A. P. H. C.*	H. M.* M. S.* E. Co.* E. Ca.	M. M.* K. P. E. H.* M. N.* M. Mc.*
Principal metastases in lung, liver or central nervous system	A. S.* R. H.* W. K.* E. M. L. B. J. L.*	M. C.* A. W.	C. T.* M. P. J. R.

* Objective remissions obtained.

cretion in patients with osteolytic metastases during consumption of a diet free of milk and cheese;[37] (5) repair of osseous metastases; (6) decreased size of soft tissue metastases; and (7) decrease in copper-resistant acid phenylphosphatase in the serum from elevated values.[25, 38, 39]

CASE MATERIAL

The series of cases represents a miscellaneous group of unselected patients, partly ward and partly private, who were admitted into this study at various stages of the spread of their disease. The pertinent features of each case, including manner of diagnosis and location of principal metastases, are summarized in table 1. All except one patient had obvious metastases, as shown by biopsy, autopsy or unequivocal radiologic signs. More than three quarters of the patients had proved refractory to other forms of therapy prior to the administration of corticoids. The extent of metastases is

TABLE 3

Status of Ovarian Function at Time of Therapy

Postmenopausal with Intact Ovaries	Radiation Therapy to Ovaries More Than 6 Months Before	Gonadectomy More Than 6 Months Before	Gonadectomy Less Than 6 Months Before
S. M. (84)	M. N. (47)*	E. H. (53)	H. M. (65)*
M. S. (70)*	A. P. (48)	C. T. (34)*	L. G. (34)*
C. C. (64)*	K. P. (43)	M. C. (40)*	M. Mc. (28)*
C. M. (75)*	M. P. (47)	H. C. (53)*	A. W. (53)
E. Co. (64)*		R. H. (42)*	F. L. (43)
A. S. (49)*		W. K. (57)*	E. M. (44)
E. Ca. (59)		J. R. (49)	L. B. (48)
M. M. (58)*			
H. B. (65)*†			
D. C. (68)			
M. B. (71)			
J. L. (59)*			

* Objective remission obtained.
† Oophorectomy after one year of treatment.

TABLE 4

Survival of 27 Patients Receiving Cortisone for at Least One Month
(As of December, 1955)

Pt.	Age This Date	Duration of Cancer Prior to Cort. Rx	Duration Cortisone Therapy	Fate
M. S.	70	6 years	*24 months	Living, in remission
C. C.	68	6½ years	*19 months	Died after 18 month remission
M. N.	47	2 years	12 months	Died after 6 month remission
E. Co.	64	6½ years	* 6 months	Died after 5 month remission
H. M.	65	2 years	*11 months	Living, in remission
R. H.	42	4½ years	* 4 months	Died after 3 month remission
E. H.	53	27 months	*13 months	Died after 11 month remission
M. C.	40	5 years	* 7 months	Living, in remission
M. Mc.	27	5 months	* 4 months	Died after partial remission of 2 to 3 months
W. K. (male)	57	5 years	* 3 months	Died after 3 month remission
C. T.	34	1½ years	* 7 months	Living, in remission
M. M.	58	2 years	3 months	Sudden death after 3 month remission
C. M.	75	4½ years	*19 months	Died after 18 months' partial benefit
L. G.	34	13 months	* 8 months	Died after 6 months' benefit
H. C.	53	3 years	3½ months	Died after 2 months' improvement
A. S.	49	18 months	6 weeks	Died; 2 weeks clearing of icterus
J. L.	59	3½ years	2½ months	Died after 1 month's improvement
H. B.	65	3 years	*18 months	Died; after 12 months benefit, disease reactivated
M. B.	71	9 years	2 months	Living; no improvement with cortisone
F. L.	48	6 months	* 2 months	Died of progressive disease
E. M.	46	15 months	* 6 weeks	Died, no benefit
L. B.	48	15 months	* 3 months	Died, no benefit
J. R.	49	9 months	1 month	Died, no benefit
A. P.	48	6½ years	1 month	Died 4 months later, no improvement
E. Ca.	59	7 years	3 months	Died, subjective benefit only
D. C.	68	13 years	6 weeks	Living, regression of nodes only
S. M.	84	24 months	6 weeks	No change in primary tumor; patient living, well 8 months later

* Receiving 15 to 120 mg. desiccated thyroid daily.

shown in table 2, and the ovarian status in table 3, at the time of initiation of therapy in these patients.

Clinical Results

1. *Survival.* Six of 26 patients with metastatic carcinoma treated for at least one month are still alive, at intervals shown in table 4. In two of these patients cortisone did not alter the slow progression of the tumor

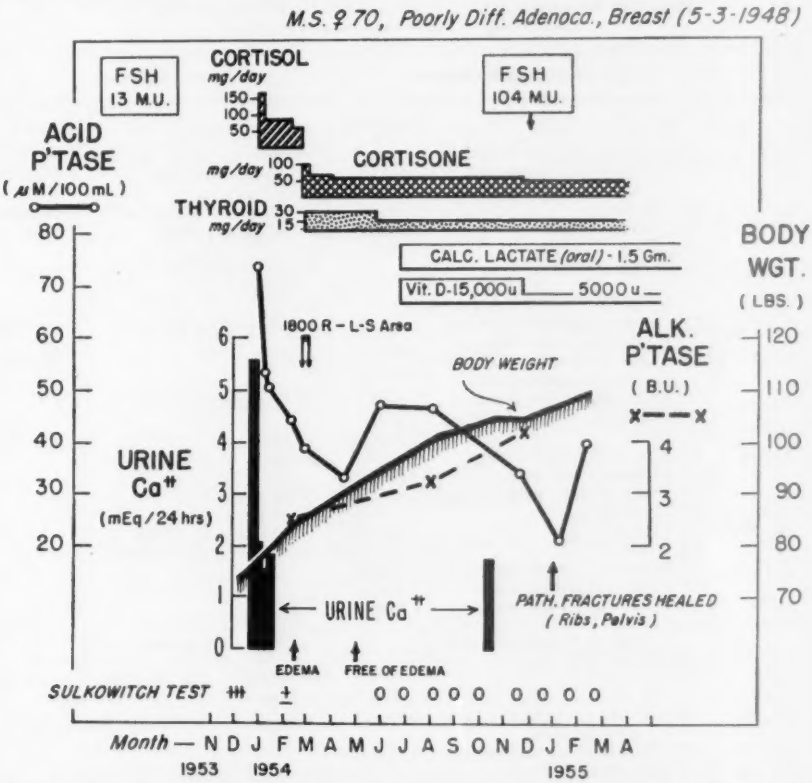

FIG. 1. Response of serum acid and alkaline phosphatase, urinary calcium excretion and body weight during remission induced by cortisone and thyroid therapy in case 1 (M. S., age 70).

growth. Three additional patients were given cortisone for shorter periods, without any evidence of subjective or objective benefit, and one elderly female (S. M.) with untreated ulcerated primary disease was treated for two months without benefit. Objective benefits, including prolonged survival, have been most frequent in patients over 60.

2. *Incidence of Remissions.* In four of seven living patients, objective remissions have appeared to contribute to survival. In an additional 14

patients (now dead), objective improvement temporarily occurred for intervals varying from two and one-half weeks in one patient whose hepatic enlargement and icterus dramatically regressed, to 18 months in two other cases. Of the 29 unselected patients with metastatic cancer treated according to our program, 18 (or 62%) improved temporarily. In 10 patients the remission of the disease continued for six months or longer, and one patient is still in remission after 37 months of treatment. No remissions more than one to two months in duration have been noted in patients with intact ovaries under 60 years of age, or in patients with previous ovarian irradiation for induction of the menopause who were less than 60 years of age.

TABLE 5

Objective Regression Noted in Metastases After Cortisone Therapy
(According to Most Important Criterion)

Pt.	Age	Soft Tissue Metastases		Osseous Metastases	
		Site	Duration Rx	Site	Duration Rx
H. M.	64	Lymphatic obstruction of arm	1 month	1st lumbar vertebra	8 months
C. T.	34	Hepatic	6 weeks	2-4th lumbar vertebrae*	6 months
M. S.	70	Cervical nodes, Skin	2 weeks 1 year	Skull, femur, pelvis	1 year
C. C.	64	None present		Lumbar spine, pelvis, femur	7 months
				Skull	1 year
C. M.	75	Slow progression of cutaneous metastases		Lumbar spine, pelvis	6 months
L. G.	35	Slow progression of cutaneous metastases		Pelvis	5 months
M. C.	40	Pulmonary lymphangitic Cervical lymph nodes	3 weeks 5 weeks	None present	
W. K.	57	Skin	2 months	Sternum	2 months
E. Co.	64	Cervical lymph nodes Pleura, chest wall	3 weeks 3 months	Subjective improvement only	
R. H.	43	Skin, pleura, mediastinum	1 month	None present	
A. S.	49	Hepatic	2 weeks	None present	
M. Mc.	27	Hepatic	2 months	Progression occurred	
E. H.	53	Skin	2–4 weeks	Subjective improvement	
J. L.	59	Cervical lymph nodes	2 weeks		
D. C.	68	Cervical lymph nodes	3 weeks		
H. B.	64	Cervical lymph nodes	1 year		
		Objective Functional Benefit		Biochemical Regression Only	
H. C.	53			Decline in acid phosphatase	1 month
M. M.	58	Return to normal ambulatory activity	6 weeks		
M. N.	47	Return to normal ambulatory activity	3 months		

* 1,000 r 250 KV irradiation in addition.

3. *Objective Improvement.* Gains of 25 to 35 pounds in weight were noted in nonedematous individuals who responded well to cortisone therapy and reflected the increased appetite (case 1, figure 1). Generally, the pa-

tients recovered their habitual weight and then ceased to gain. Return of hemoglobin and erythrocyte concentration to normal levels was noted concurrently in these patients. In only two cases was there an unusual increase in weight, which accompanied progressive hepatic metastases and signs of hypercortisonism.

In eight patients with osteolytic metastases it was possible to follow the excretion of calcium in the urine. In four patients a rapid decrease of urinary calcium was noted, commencing after a few days of treatment (figure

TABLE 6

Endocrine Pathology and Response to Cortisone Therapy

Remission	Pt.	Age	Ovarian Pathology	Adrenal Cortical Pathology
A. None	A. W.	53	Unilateral cortical stromal hyperplasia	*Nodular; metastatic cancer
	L. B.	48	Radiation reaction; slight cortical stromal hyperplasia	
	F. L.	44	Cortical stromal hyperplasia	Metastatic cancer
	E. M.	44	Negative	*Nodular hyperplasia
	J. R.	49	Negative; corpus luteum	*Nodular; metastatic cancer
	M. P.	47	Grossly normal	*Negative
B. 2–18 month remission	C. C.	64	*Metastatic cancer	*Atrophic; metastatic cancer
	E. C.	64	*Metastatic cancer; cortical stromal hyperplasia	*Atrophic; metastatic cancer
	H. C.	53	Metastatic cancer	*Atrophic; nodular
	E. H.	53	Cortical stromal hyperplasia	*Atrophic; metastatic cancer
	L. G.	35	Cortical stromal hyperplasia; luteinization consistent with polycystic ovaries; metastatic cancer	*Atrophic; metastatic cancer
	R. H.	43	Cortical stromal hyperplasia, and fibrosis	—
	M. Mc.	27	Stein-Leventhal type of polycystic luteinized ovaries	*Metastatic cancer
	H. M.	64	Thecoma; cortical stromal hyperplasia	
	C. T.	34	Follicle cysts and corpora lutea	—
	H. B.	64	*Atrophic, intact stroma	*Atrophic; metastatic cancer
	D. N.	47	*Metastatic cancer	*Atrophic; metastatic cancer

* After therapy.

1). Negative Sulkowitch's tests of the urine persisted for as long as 18 months in one patient in spite of a high calcium diet during the latter part of the remission. Recalcification of osteolytic metastases occurred in this patient, as in two others in whom calciuria decreased during therapy.

Recalcification of osteolytic metastases was not definite until after at least three months of treatment, and it occurred in several of our patients whose remissions exceeded this period and who had generalized osteolytic disease. In the two longest remissions (24 and 37 months, respectively), there was a widespread repair of bone, including many areas which had never received x-ray irradiation (table 5, figure 2). Ambulatory activity

FIG. 2. Recalcification of cranial metastases in C. C., age 64. (*Above*) Skull film obtained prior to cortisone and thyroid therapy. (*Below*) Skull film obtained after 11 months of cortisone therapy. Patient in complete remission from signs and symptoms of disease. (Case reported in detail in reference 22.)

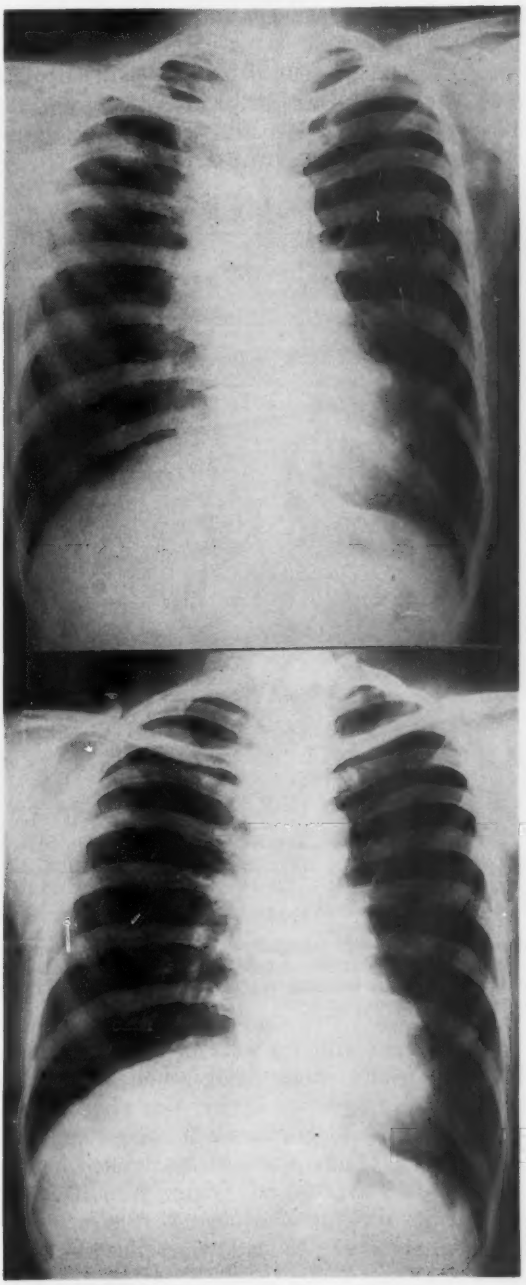

FIG. 3. Alteration in pulmonary infiltrations noted in M. C., age 40, during five weeks of therapy with cortisone. Biopsy of right supraclavicular lymph node revealed metastatic carcinoma just prior to first film on April 29, 1955.

was restored to normal in seven patients, without the use of any x-irradiation in five (table 2).

Reduction in size of lymph nodes, pulmonary infiltrations and pleural effusions have been noted after commencement of therapy in these and other patients (figure 3). In several instances cutaneous metastases have also been arrested. In two cases with hepatic metastases there was objective im-

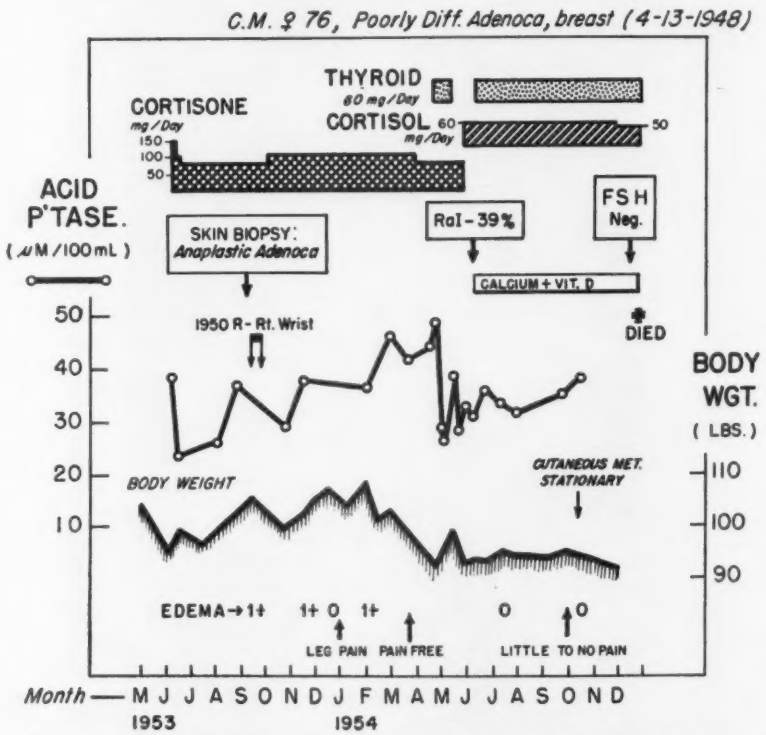

FIG. 4. Reduction of serum acid phosphatase activity noted initially in C. M., age 76, after cortisone therapy, and subsequently when thyroid substitution therapy was initiated. Diffuse osteolytic metastases were present, which showed some recalcification by December, 1953, after six months of cortisone therapy.

provement of liver function within a week of commencement of treatment, although in one of these intravenous nitrogen mustard therapy was concurrently administered.

Copper-resistant acid phenylphosphatase in the serum, normally less than 22.3 micromoles phenol/100 ml., was initially elevated in 15 out of 25 patients tested, averaging 33 μM/100 ml. (range, 6 to 100). A further rise occurred in six of eight patients who did not receive prolonged objective benefit. In 12 of the remaining patients, who otherwise received objective

palliation, phosphatase activity fell to a mean of 21 μM/100 ml. during remissions (figures 1, 4). The duration of the suppression of serum acid phosphatase activity usually was closely related to the duration of the remission, with values subsequently exceeding pretreatment levels, when the tumor reactivated (averaging 49 μM/100 ml. in 15 patients). Administration of cortisone or ACTH per se does not affect the level of serum acid phenyl-

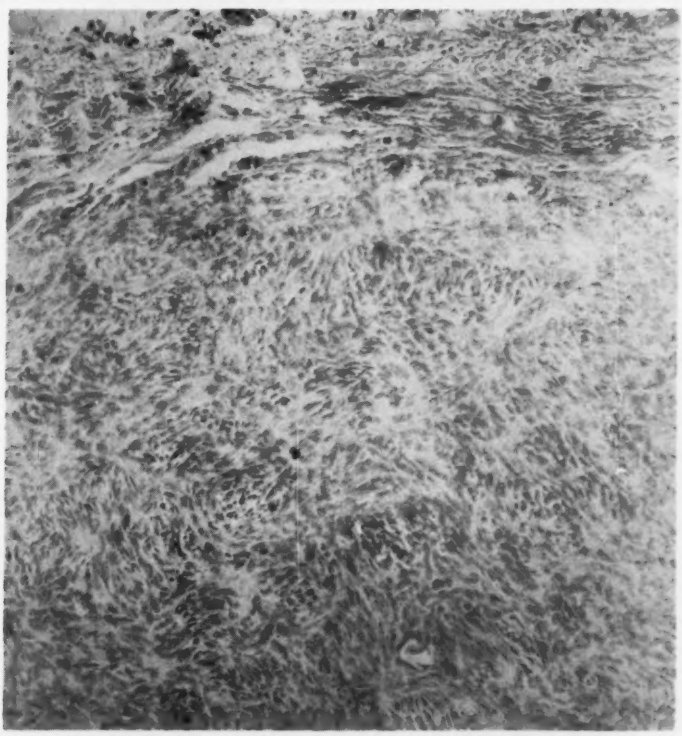

FIG. 5. Ovarian cortical stromal hyperplasia in case 3 (H. M., age 64). (×250.)

phosphatase with this technic. Serum alkaline phosphatase was within normal limits during many of these acid phosphatase analyses, except when liver metastases were present.

4. *Ovarian Pathology and Response to Cortisone Therapy.* Previous studies have indicated an especially unfavorable prognosis in patients whose ovaries do not show cortical stromal hyperplasia.[10] In this small series of cases it is apparent that patients whose ovaries appear relatively normal histologically, in view of the patient's age and menstrual activity, are not so likely to respond to cortisone therapy as those whose ovaries show either metastases or marked cortical stromal hyperplasia (table 6, figure 5). Of

12 patients with abnormal ovaries, nine showed remissions, whereas two out of three patients with "negative" ovaries showed rapidly fatal disease. In two other patients with progressive disease, unilateral or minimal cortical stromal ovarian hyperplasia was present. In one of the patients resistant to oophorectomy and cortisone therapy (E. M., age 44), a nodular hyperplasia of the adrenal cortex was noted at autopsy, suggesting that cortisone in doses up to 300 mg. daily had had little suppressive effect upon the adrenal in this patient.

5. *Clinical Evidence of Estrogen Deprivation.* Hot flashes appeared within several weeks in a number of surgically castrate patients (table 7).

TABLE 7

Estrogen Withdrawal Symptoms Induced by Cortisone Therapy in Patients with Mammary Carcinomas

Remission	Pt.	Age	Menopause			Duration of Absence of Hot Flashes	Effect of Cortisone Therapy	
			Type	Hot Flashes + monthly ++ weekly +++ daily	Duration		Reappearance of Hot Flashes	Maintenance Dose Required
A. None	S. M.	84	Spont.	++	Persistent	Persistent	Exacerbation +++ 2–3 weeks	50–75 mg.
	E. M.	46	Surg.	+	2 months	Persistent		
	J. R.	49	Surg.	+++	3 months	Persistent		
	F. L.	42	Surg.	+++	(given estrogen)	(given estrogen)	After 4–5 weeks +++	75 mg.
B. Partial to complete	L. G.	35	Surg.	++	10 days	1 month	After 6 weeks +++	200 mg.
	H. C.	53	Surg.	+	Months	4 months	After 6 weeks +	100 mg.
	E. H.	53	Surg.	++	2 years	1–2 years	After 3 weeks	100 mg.
	M. C.	40	Surg.	+	3–4 years	1 year	After 10 days ++	100 mg.
	R. H.	43	Surg.	None	—	1 year	After 6 weeks +++	100 mg.
	C. T.	34	Surg.	++	Months	6 months	After 3 weeks +++	75–100 mg.
	H. M.	65	Spont.	++	2–3 years	12 years		
			Surg. cast	+++	1 week	1 month	After 6 weeks +++	75 mg.
	H. B.	64	Spont.	++	11 years	Persistent	Exacerbation +++ after 4–6 weeks	100 mg.
			Surg. cast	+++	Months	Persistent	Persistent	100 mg.
	E. C.	64	Spont.	None	—	15 years	None	—
	C. M.	75	Spont.	++	6 years	25 years	None	—
	M. S.	70	Spont.	None	—	18–20 years	None	—
	C. C.	64	Spont.	None	—	15 years	None	—

In some remissions there appeared to be a definite correlation between frequency of these symptoms of estrogen withdrawal, relief of pain and improvement in appetite and well-being. Hot flashes were not induced in patients whose ovaries were intact, regardless of age. In most castrate patients hot flashes occurred transiently after oophorectomy, and re-appeared after from three to six weeks of cortisone administration. In a few castrate patients, progressive cancer metastasis occurred in spite of continued hot flashes; and in some of the noncastrate elderly patients, prolonged remissions occurred without any such symptoms.

6. *Influence of Cortisone upon Pituitary Function.* Urinary follicle-stimulating hormone (FSH) in postmenopausal or oophorectomized pa-

tients with breast cancer has usually been in the low or normal adult range before treatment, with values ranging from 6 to 26 mouse units (m.u.). During cortisone therapy, FSH excretion increases to 106 to 211 m.u., persisting at this level for periods of up to 24 months (table 8). Cortisone and ACTH induce in premenopausal patients a transient increase in FSH excretion, lasting only a few weeks.[15, 16, 19, 20] Cortisone and cortisol are believed to be metabolically interchangeable in ability to inhibit ACTH secretion.[40]

TABLE 8

Effect of Cortisone Therapy upon Excretion of Pituitary Follicle-Stimulating Hormone

History of Menopause	Pt.	Age	Urinary Follicle-Stimulating Hormone, mouse units (m.u.)/24 hr.			
			Pre-treatment	Interval	During Treatment	Remission
A. Spontaneous, years previously	E. C.	64	6.6	3 mos. 4 mos.	106 211	Present Relapse
	C. C.	64	106	6 mos.	106	Present
	M. S.	70	13	10 mos. 24 mos.	106 53	Present Present
	H. B.	64		12 mos. 18 mos.	52 6.6	End of remission period In relapse
B. Surgical castration, at least 1–3 mos. before	M. C.	40	211	2 wks. 6 mos.	26.4 6.6	Present Relapse
	C. T.	34	13.2	6 wks. 6 mos.	106 106	Present Present
	R. H.		26	6 mos.	106	Present
	M. Mc.	27	6.6	2 wks. 5 wks. 4 mos.	26.6 17.6 6.6	Minimal Minimal Relapse
	H. C.	53	—	2 mos.	104	Brief remission
	H. M.	64	106	9 mos.	211	Present

7. Tumor Pathology and Response to Cortisone Therapy. Most of the cancers responding to cortisone administration in this series were classified as carcinoma simplex at the time of original operation or at the time metastases were biopsied. We have therefore been unable to establish any relationship between the histologic type of tumor and likelihood of response. In one patient with ovarian stromal hyperplasia (F. L.), no remission was achieved in the growth of an inflammatory carcinoma of the breast, and a second patient (R. H.) relapsed when inflammatory metastases appeared in the remaining breast.

8. *History of Previous Remissions after Endocrine Therapy.* Eight out of nine patients with prior remissions of their disease as a result of testosterone, cortisone (one case), stilbestrol therapy (one case) or oophorectomy subsequently responded gratifyingly to cortisone. Cortisone was wholly

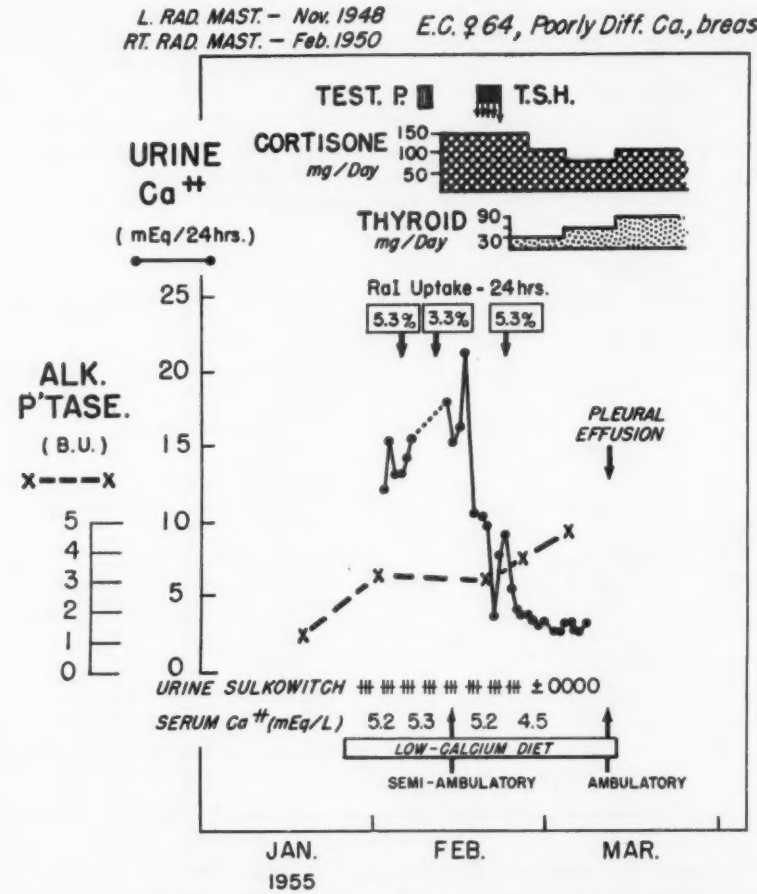

FIG. 6. Urine calcium excretion in case 2 (E. C., age 64), with diffuse osteolytic metastases. Note concurrent reduction with commencement of thyroid therapy in addition to cortisone.

ineffective in three out of five patients who had not responded to other endocrine therapy, and it gave only minimal benefit in the other two patients.

9. *Role of Thyroid.* Desiccated thyroid was administered as an adjunct to cortisone in 16 patients in this series, usually weeks or months after beneficial results had been observed from cortisone administration. Most of our patients with long remissions received 15 to 120 mg. per day (table 4).

Although cortisone was the agent producing initial major benefit, in some instances it was clear that thyroid supplementation was of importance: (1) in one patient with proved myxedema (E. C., case 2), whose clinical manifestations were accentuated at the onset of cortisone therapy and whose urinary calcium excretion (on a low calcium diet) did not fall to a normal low range until 30 mg./day of desiccated thyroid had been started (figure 6); (2) in two patients (M. S., case 1, and C. M.) whose persistent 2 plus ankle edema, brought on by cortisone therapy, permanently disappeared after spontaneous diuresis, beginning a few weeks after thyroid supplementation; (3) in a third patient (C. M.) in whom a persistent decrease in serum acid phenylphosphatase occurred after thyroid supplementation was started (figure 4). In view of the frequent occurrence of microfollicular atrophy of the thyroid in advanced cancer of the breast,[9] latent or overt myxedema might be anticipated in all cases in whom occur such suggestive clinical manifestations as edema, lethargy, cold intolerance, etc. Scattered observations of radioiodine uptake in patients in this series have thus far revealed only two patients with true thyroid insufficiency before or after therapy with cortisone.

10. *Toxicity and Side-Effects.* The infrequent occurrence of side-effects or toxic manifestations after prolonged cortisone treatment has been noteworthy in this series. Only two patients, aged 27 and 35, in one of whom maintenance doses of cortisone of necessity exceeded 100 mg. daily, showed Cushing's facies after two or more months of treatment. Both patients died with very extensive liver metastases, so that less cortisone than usual may have been inactivated by the liver.[41] None of the elderly patients (all of whom sooner or later received thyroid) developed dependent edema, congestive failure or other stigmata of sodium retention, in spite of a liberal sodium intake in most instances. One patient developed diabetes mellitus without ketosis, which was well controlled on 20 units of protamine zinc insulin daily and which subsequently disappeared when cortisone was discontinued after 18 months' therapy. Exacerbation of essential hypertension has not occurred in this series of patients, nor have any patients developed peptic ulcers proved by x-ray during treatment. One patient (case 2), after five months of cortisone treatment, had a massive, nonfatal gastrointestinal hemorrhage from carcinomatous invasion of the duodenum by metastases. Recurrent pulmonary infections were noted after more than a year of treatment in one patient, with adrenocortical insufficiency complicating the first pneumonic episode. Another patient died from probable adrenocortical insufficiency when cortisone was unwisely withdrawn at another hospital without adequate supplementation with ACTH. Two patients developed seizures while receiving cortisone, with cerebral metastases ultimately proved at autopsy in one case and clinically diagnosed in the other.

Unlike therapy with male or female sex hormones, we have not observed any stimulation of neoplastic disease by cortisone or administration of thyroid.

11. *Cortisone Therapy in Other Types of Cancer.* Subjective and objective palliation of metastatic endometrial cancer, adenocarcinoma of the male breast, pharyngeal undifferentiated carcinoma with lymphoid elements and thyroid carcinoma has been observed in single instances, each following the therapeutic plan outlined above. No definite remissions have been seen in metastatic carcinoma of the colon, pancreas or uterine cervix.

Discussion

These studies emphasize that cortisone therapy has a place in the treatment of advanced cancer of the breast, contrary to some of the early reports in the literature,[20, 22] and corroborating other reports.[23-26, 38, 39] The divergence of these results from those obtained by some observers may be accounted for in part on the basis of complete eradication of ovarian function in many of our patients, use of moderate dosage of cortisone, persistence in therapy for more than a few weeks, and reliance insofar as possible upon multiple objective methods of estimation of remission from changes in body weight, calcium excretion, copper-resistant serum acid phenylphosphatase, and serial radiologic observations. In several reported series, both cortisone and ACTH therapy have been included in the study, in spite of their diametrically opposed actions on the adrenal cortex.[20, 22] We have utilized cortisone for the restoration and maintenance of ambulation in our series of patients, many of whom were initially partially but seldom wholly bed-ridden. In our experience, recalcification of osseous metastases is seldom demonstrated after any type of therapy if the patient is unable to resume ambulatory activity, since calcium metabolism is already unfavorably affected by confinement to the horizontal position.[42]

Our observations are in general agreement with those initially obtained by West et al. at the Memorial Cancer Center concerning the percentage of patients responding favorably to high doses of cortisone. In their studies, elimination of the possible ovarian source of estrogens has been practiced as a necessary adjunct to therapy in younger patients.[28] As far as response of patients is concerned, adrenalectomy appears to have little advantage over cortisone therapy,[39] since about one-half of patients respond in either instance, and the older patients are usually more apt to respond.[4, 43]

It is our impression that enhanced hypophyseal gonadotrophin secretion is one of the uncontrolled factors during cortisone therapy causing relapse of patients, possibly as a result of gonadotrophin stimulation of cellular elements in the zona fasciculata and zona reticularis of the adrenal cortex in oophorectomized patients.[44] In postmenopausal females with intact ovaries, cortisone therapy would surely tend to augment ovarian estrogen production and result in stimulation of estrogen-sensitive tumors.

Thyroid supplementation appears to have had a definite effect in prolonging remissions, either through its synergistic inhibitory effect upon the adenohypophysis or through its peripheral metabolic action in preventing un-

favorable tissue changes, such as local myxedema, brought about by prolonged cortisone therapy. The incidence of side reactions attributable to cortisone has been low in this series of patients, nearly all of whom have received thyroid supplementation after a few weeks or months of cortisone treatment. Cortisone therapy in hypophysectomized rats appears to be antagonistic to thyroid-stimulating hormone.[45] Other studies indicate that cortisone exerts a direct suppressive action upon thyroid uptake of iodine,[32] without altering the peripheral rate of thyroxine degradation.[46] Numerous observers have commented upon the reciprocal interdependence of thyroid hormone and corticoids in replacement therapy of patients with anterior hypophyseal insufficiency.[33] Recently, Loeser has reported that thyroid hormone therapy appears to have had some effect in inhibiting metastases in various human neoplasms.[47] Microfollicular atrophy of the thyroid gland, noted in two thirds of mammary cancer patients at autopsy by Sommers, is deserving of much further study. Cortisone therapy in one patient in this series precipitated clinical myxedema, and urine calcium excretion did not fall to normal in this case until thyroid supplementation was started (case 2).

It is obvious that in patients over 65 ovarian function may be so reduced by metastases or senescence that excellent palliation is possible by cortisone therapy without oophorectomy. However, no prolonged remissions have been induced by cortisone therapy in patients under 60 with intact ovaries. Only in the older age group, therefore, it is justifiable to rely solely upon cortisone therapy for suppression of the production of endogenous sex hormone. The absence of estrogen withdrawal symptoms in all elderly patients with intact ovaries thus treated strongly suggests some continued function by the gonad, and therefore a continued hazard of possible endocrine-induced reactivation of the tumor.

Subjective palliation of prostatic carcinomatous metastases has been reported with use of cortisone in castrate patients, but objective evidence of remission has seldom been reported.[48] The benefits seen in patients with cancer of the breast and prostate are consistent with altered adrenocortical activity produced by cortisone administration to patients with intact pituitary adrenocortical mechanisms. There is some evidence, however, that cortisone may interfere with the activity of estrogens in stimulating target tissue metabolism.[49]

Unlike castration in the male, which is highly effective in temporarily controlling metastatic prostatic cancer in 75 to 80% of cases, castration alone in the female is relatively ineffective in producing remissions in mammary cancers. Only about 15 to 45% of castrate females show objective benefit,[3, 48] although possibly some increase in longevity results.[50, 51] After castration, continued secretion of biologically active estrogens continues.[11, 12] Our observations thus far are consistent with the hypothesis that in most patients with breast cancer the hyperplastic ovary is the most important source of sex hormone stimulating or supporting tumor growth. Cortical

stromal hyperplasia appears to be a manifestation of its abnormal activity in this respect. After oophorectomy, only very temporary benefit usually occurs, because of a compensatory increment in adrenocortical production of sex hormone, manifested by rapid disappearance of estrogen withdrawal symptoms (hot flashes), at times within seven to 10 days of operation. This may result from stress-induced increase in pituitary ACTH secretion, resulting in secretion of additional C19 as well as C21 steroids from the adrenal cortex,[52] or from altered rates of gonadotrophin secretion following castration which stimulate liberation of estrogen from the adrenal cortex.[44, 53-55] Cortisone appears to be highly effective in suppressing further adrenal cortical production of sex hormone in most instances, suggesting that the ACTH pathway is most important.

There appears to be a small percentage of patients with breast cancer without ovarian disease but with distinct hypertrophic changes in the adrenal cortex [9] in whom cortisone therapy, even in large doses, is unable to induce adrenocortical atrophy. These patients may continue to have some type of pituitary activation of adrenocortical function, and adrenalectomy or hypophysectomy may be the only means of removing endocrine stimuli for cancer growth. These concepts should be tested in practice because of the serious medical, economic and social factors implicated in major surgical attack upon the hypophysis and adrenal cortex; if prolonged palliation by therapy with sex hormones or oophorectomy or both, followed by cortisone with thyroid, is productive of maximal benefit in the majority of endocrine-dependent cancers of the breast, surgical procedure may be concentrated upon those with the more resistant endocrine secretory patterns whose disease progresses in spite of these medical measures.

Summary

Experience is summarized concerning cortisone inhibition of advanced mammary cancer covering over 13 patient-years of treatment in 30 cases. Since cortisone in maintenance doses of 50 to 100 mg. suppresses adrenocortical secretory activity and augments pituitary gonadotrophin excretion, ovarian function must be absent if estrogenic endocrine secretion is to be reduced and remissions are to be anticipated. Amenorrhea induced by x-radiation appears insufficient for this purpose, and oophorectomy must supplement cortisone therapy in patients under 65 to 70 years of age. Cortisone may be effective as an initial form of treatment of inoperable disease, or as a treatment of last resort, when x-radiation of the tumor and sex hormone therapy are no longer effective. Prolonged remissions are most often seen in patients over the age of 60—or oophorectomized more than six months before—with ovarian cortical stromal hyperplasia or metastases.

Objective palliation has been observed lasting as long as 18 to 37 months in 62% of all cases, with osseous repair in 24%. There is some indication that thyroid therapy to maintenance doses of 15 to 120 mg. produces pro-

longed remissions by minimizing the side-effects of cortisone treatment and reinforcing the tumor-suppressive action of cortisone. Although cortisone and thyroid may act chiefly through inhibition of the pituitary gland to reduce production of adrenal cortical sex hormone, the possibility exists that they function antagonistically to estrogenic stimulation of the target organ.

Case Report

Case 1. Mrs. M. S., 70, was referred by Dr. Frank Barton in December, 1953, for treatment of diffuse osteolytic metastases from cancer of the breast. The patient had been essentially well until November, 1947, when a lump developed in her breast. On May 3, 1948, right radical mastectomy was performed by Dr. Barton, who removed a poorly differentiated adenocarcinoma with metastases to six of nine axillary lymph nodes. The patient was given postoperative x-ray therapy and was well until August, 1952, when Bell's palsy developed. During 1953 the patient lost 50 pounds in weight and developed increasingly severe pains in her back, right hip and arms. Protuberant masses developed over her cranium in the frontal and parietal areas, as well as enlarged cervical lymph nodes, and a cutaneous lesion on the left second toe. The patient weighed 75 pounds. Diffuse osteolytic disease was present by x-ray throughout the skeletal system, with some compression deformity of C5, C6, D7 and D10. A small amount of fluid was present in both pleural cavities. The hematocrit was 35%; hemoglobin, 10.9 gm.%. On a low calcium diet she excreted 5.6 mEq./24 hrs. of calcium, and her serum acid phosphatase (copper-resistant) was 74 μM/100 ml. (upper normal limit, 22.3 μM). Serum phosphorus was 5.4 mg.%; alkaline phosphatase, 2.1 Bodansky units (figure 1). Serum albumin was 3.6 gm.%; serum globulin, 3.6 gm.%.

On January 1, 1954, the patient was given 160 mg. daily of hydrocortisone for two days, followed by maintenance therapy of 80 mg. daily, with 1.2 gm. potassium citrate orally to supplement her diet, and 50 mcg. vitamin B_{12} orally daily. Five days after hydrocortisone was started the serum acid phosphatase declined to 54 μM and the urinary calcium to 1.5 mEq./24 hrs., and subjectively the patient's pains and appetite were much improved. At this time serum phosphorus decreased to 3.8 mg.%; alkaline phosphatase later rose to 4.2 Bodansky units. After two weeks of treatment the principal cervical lymph node was no longer palpable, and within six weeks the cranial bossing had receded to normal.

Between February 19 and 27, 1954, 1,800 r radiation therapy was administered to the lumbosacral area for pain resulting from pathologic fractures of the right pubic ramus. The patient was then ambulatory, having gained five pounds in weight, with some mild ankle edema. At this time she was shifted to cortisone maintenance therapy, which was slowly decreased to a 50 mg. daily dose, and 15 mg. of desiccated thyroid were henceforth administered. After June 20, 1954, she had no further edema of the ankles or pain from her osseous metastases. At this time, her urine calcium having been consistently negative by Sulkowitch's test, supplementary calcium lactate, 1.5 gm. daily, and 15,000 units of vitamin D_2 in propylene glycol, were started. For the next year and a half Sulkowitch's tests of her urine continued negative, and her weight increased to a plateau of 109 pounds by February, 1955, at which time her hemoglobin returned to normal. The patient resumed a very active social life.

The cutaneous toe lesion regressed to a fibrotic area in December, 1954. Increased radiologic density of numerous osseous metastases was noted in December, 1954, with additional repair of cranial, lumbar spinal and femoral lesions noted by June 9, 1955, and again on May 8, 1956. As of December 16, 1955, the lymphadenopathy and cutaneous metastases have completely regressed; one small (1.5 cm.)

osseous protuberance remains in the left parietal area of the cranium, and no new metastases have developed anywhere in soft tissues or bone in the past two years. In the past year she has had no bone pains referable to her tumor, and has carried on an active ambulatory life, with her weight stable at 108 to 110 pounds. Her serum acid phosphatase (copper-resistant) continues somewhat elevated, at 52 μM/100 ml.; the serum alkaline phosphatase has been normal throughout. (*Note:* Patient remains in good health as of February 7, 1957.)

Summary: This patient presents a striking example of objective remission, without prior therapy, and with sole use of low maintenance doses of hydrocortisone in the early months of treatment.

Case 2. Miss E. C., 64, was admitted for treatment of crushing substernal distress of one day's duration. Past history revealed a menopause without hot flashes 14 years before, and essential hypertension diagnosed 12 years before. After symptoms of six months' duration, a left radical mastectomy for poorly differentiated carcinoma was carried out in November, 1948, with negative lymph nodes. A right radical mastectomy for carcinoma, possibly a second primary, was performed by Dr. K. B. Lawrence in February, 1950. Subsequently, a diagnosis of hypothyroidism was made elsewhere on the basis of a basal metabolic rate of minus 33, and thyroid substitution therapy had been taken intermittently. The substernal distress had developed after the patient resumed thyroid medication following a three-month lapse in therapy. Examination disclosed generalized osteolytic metastases, infraclavicular and cervical lymph node metastases, faint heart sounds and a pericardial friction rub. Serial T wave changes occurred during the first month of bed-rest for a suspected myocardial infarct. No thyroid or iodine-containing medication was initially administered.

Hormonal therapy for her breast metastases was commenced February 7, 1955, while the patient was on a low calcium diet. Calcium excretion studies are presented in figure 6. Immediately upon receiving testosterone propionate the patient's osseous complaints and anorexia grew worse, and her serum acid phosphatase reached 67.0 μM/100 ml. Cortisone, 150 mg. per day, was started on February 12, 1955. Although slight subjective improvement was noted, abnormally large amounts of calcium continued to be excreted during the next week. During this time the patient's lethargy and anorexia appeared to increase, and repeated radioiodine uptakes by the thyroid revealed minimal iodine concentration, even after 20 mg. of Armour thyrotropic hormone daily for five days (figure 6). When 30 mg. per day of thyroid hormone were commenced on February 24, 1955, there was a prompt improvement in the patient's energy, appetite and ability to ambulate, and a sustained decrease of urine calcium excretion to minimal levels. Serum calcium values also decreased, and her alkaline phosphatase activity increased from 1.3 to 4.7 Bodansky units. During the patient's hospital stay her hemoglobin and hematocrit gradually decreased from normal values to 9.6 gm./100 c.c. and 32%, respectively.

On maintenance doses of 100 mg. per day of cortisone and gradually increasing desiccated thyroid intake (up to 90 mg. per day), the patient convalesced well, except for a left pleural effusion which complicated her course on March 12, 1955, when her serum acid phosphatase was 59 μM/100 ml. The cervical and infraclavicular lymphadenopathy regressed almost completely during the first three weeks of treatment. Only one or two questionable hot flashes were noted prior to her discharge to a convalescent home on March 25, 1955. During April and May, 1955, her serum acid phosphatase reached minimal values of 33 to 36 μM/100 ml., and she had no hot flashes.

Pleural effusion was readily controlled by only two paracenteses in three months, mercurial diuretics and sodium restriction. Hepatic enlargement was first noted on

May 27, 1955, after three and one-half months of excellent improvement. Late in June, 1955, the patient attempted to return to part-time work, although she had not been able to gain any weight beyond 100 pounds, and her serum acid phosphatase had risen to 50 μM/100 ml.

Increasing anorexia, dyspnea and fatigability occurred during July, 1955, with massive hematemesis on July 29, 1955. Both lung fields displayed prominent, fan-shaped hilar infiltrations suggestive of lymphangitic metastases and bilateral effusions. The liver was no more enlarged than it had been during the previous two months. Pericardial friction rub was present, with an electrocardiogram suggestive of pericarditis. The patient died on July 31, 1955.

Autopsy disclosed that terminal gastrointestinal bleeding resulted from pancreatic metastases perforating into the duodenum. Diffuse metastases were present in lung parenchyma, liver, pancreas, adrenals, pituitary, thyroid, intestines, bladder serosa, uterine myometrium and bone. The ovaries were largely replaced by metastases but also showed residual evidence of marked cortical stromal hyperplasia. The tumor cells were generally in an adenocarcinomatous arrangement.

Summary: This patient represents an example of objective partial benefit from therapy, in which thyroid therapy appeared important in the reduction of hypercalciuria. Failure to obtain more lasting benefit does not seem attributable to residual ovarian function in view of her gonadotrophin response (table 8).

Case 3. H. M., age 65, had been essentially well until two years prior to admission, when a right radical mastectomy was performed for carcinoma arising in aberrant breast tissue in the right breast with negative lymph nodes. She had had a spontaneous menopause about 15 years previously, with hot flashes intermittently thereafter for several years. A hysterectomy had been performed about 14 years before for postmenopausal bleeding, with removal of a fibroid uterus. The postoperative course was uneventful save for some edema of the right arm and hand. Eighteen months following operation the patient noted onset of aching pains in the vicinity of the neck, both shoulder girdles and low back, which necessitated terminating her employment as a stitching machine operator. She was treated for arthritis by her physician with three tablets a day of cortisone, with marked relief, and subsequently returned to work. Cortisone was discontinued one month prior to admission, however, because of increasing edema of the right arm and hand and both legs developing after a long auto ride. When first seen the patient was obese, with marked pitting edema of both legs and right arm and hand. On admission to Dr. William E. R. Greer's service, December 20, 1954, bilateral tenderness of the calves was noted, and the patient was placed on anticoagulant therapy with heparin. Circulation time (arm-tongue) was 12 seconds, and venous pressure 165 mm. saline. Hemoglobin was 11.9 gm.; hematocrit, 42%. Urine showed 1 plus albumin, with specific gravity of 1.015 to 1.017. Total serum protein was 6.2 gm., with 3.7 gm. albumin and 3.5 gm. globulin; serum electrolytes were within normal limits. The patient's 24 hour radioiodine uptake was 40.4% of the administered dose, and serum protein-bound iodine was 3.8 μg%. Urinary follicle-stimulating hormone excretion was positive at 105.6 m.u. per 24 hours; 17-ketosteroids, 3.5 mg. per 24 hours. A metastatic x-ray series showed an enlarged sella turcica, with possible erosion of the floor and osteolytic areas in the left clavicle, twelfth dorsal vertebra, first lumbar vertebra (with slight collapse), and right humerus and femur. Copper-resistant serum acid phosphatase was 28.6 micromoles phenol per 100 ml. (upper normal limit, 22.3). On December 27, after a week of bed-rest, this value fell to 13.7 micromoles.

On January 4, 1955, bilateral oophorectomy was performed by Dr. Charles W. Robertson. The left ovary showed a large thecoma, 1.2 cm. in diameter, and both ovaries had a yellowish rind 2 mm. in thickness, indicative of moderate cortical stromal hyperplasia (figure 5). The thecoma showed much more than the usual amount of gross lipoid.

By January 10 the patient was having nocturnal hot flashes, and all pains in the back and shoulder girdle had remitted but occipital headaches had not; however, acid phosphatase activity rose sharply (to 36.8 micromoles), and at the time of her discharge, on January 12, 1956, the hot flashes had ceased. Her weight was 160 pounds on discharge, with minimal residual ankle edema after subsidence of her bilateral thrombophlebitis. During the ensuing three weeks the patient developed recurrent pains in occiput, arms and back, and was able to resume only a semi-ambulatory activity because of weakness. Edema of the right arm and hand persisted. Therefore, on January 29 she was started on 200 mg. of cortisone, followed by 100 mg. daily for one week, and then on a 75 mg. daily maintenance dosage, with 60 mg. of desiccated thyroid daily, and 0.6 gm. potassium chloride three times daily.

During the next three weeks there was a marked improvement in appetite and strength, the patient being able to resume some of her housework. There was complete relief of all skeletal aches except for those involving the terminal phalanges, where she had hypertrophic arthritis. There was only a transient increase in swelling of the right arm, which had subsided by February 26. Edema of the ankles did not recur. During the latter part of March the patient noted recurrence of hot flashes several times weekly, at which time her excretion of follicle-stimulating hormone was 105.6 m.u., negative at 211 m.u. On March 26 she was asymptomatic, weighed 165½ pounds without pedal or brachial edema, and her hemoglobin was 14.3 gm.%. At this time cortisone was reduced to 62.5 mg. per day, with immediate cessation of hot flashes and recurrence of bone pain. Increasing the cortisone dose to 100 mg. per day resulted in immediate control of pain, with a recurrence of hot flashes by April 26. Thereafter, dosage of cortisone was usually 75 mg. per day. At this time the patient's daughter volunteered that her mother performed more housework than she did herself. During May the patient returned to her factory job. Early in June the patient went two weeks without hot flashes, with coincidental return of pain in the neck and shoulder, although dosage of cortisone was unchanged. Desiccated thyroid was increased to 120 mg. daily. By August 25, 1955, her weight had increased to 175 pounds, although there was only a trace of edema of the feet or right arm. During and after a hurricane, fatigability and excessive somnolence occurred for one or two days. Because of epigastric distress for several weeks thereafter, an upper gastrointestinal x-ray series was performed, which was negative. On November 18, 1955, the first lumbar vertebra was observed to be denser and of more regular outline than previously. Hot flashes were absent during November and December, but bone pains did not recur. During this time, however, serum acid phosphatase gradually increased to pretreatment levels. On January 3, 1956, her edema-free body weight was 188 pounds, and physical examination was negative save for excessive obesity. Urinary follicle-stimulating hormone excretion was 211 m.u. at this time. Dexedrine and a low calorie diet were prescribed, and her weight on March 6, 1956, was 183 pounds, with only a trace of edema of the right arm. At this time complete metastatic x-ray series failed to reveal any progression of bone disease. However, hot flashes were absent for three weeks, and the patient had begun to note recurrent, rather severe pains in her neck and shoulders. For several months random Sulkowitch's tests of the urine were 2 plus, so a synthetic androgen was added to her therapeutic régime, with resultant control of symptoms for the next two months, during which time she continued at work. (*Note:* Patient remains in good health, employed full time, as of February 7, 1957.)

Summary: This patient represents a striking example of postmenopausal ovarian hyperplasia, associated with enlarged sella turcica and an unusually high pretreatment gonadotrophin excretion (table 8). Cortisone therapy was beneficial before and after oophorectomy, and the dosage was definitely related clinically to manifestations of estrogen deprivation after surgical castration.

SUMMARIO IN INTERLINGUA

Le duo principal fontes de estrogenos in femininas es le ovarios e le cortice adrenal. Studios pathologic e biochimic suggere que in patientes con cancere mammari le ovarios continua un longe tempore post le menopause lor secretion de estrogenos e que isto pote esser terminate solmente per ovariectomia. Le administration de cortisona in doses de 50 a 100 mg se ha monstrate capace a effectuar alterationes atrophic in le cortice adrenal e a reducer le excretion adreno-cortical de estrogenos, sed iste processo pote esser de beneficio clinic in patientes con metastatic cancere mammari solmente si le presentia de estrogenos ovarian ha previemente essite eliminate per le execution de ovariectomia in le caso de individuos de minus que 65 annos de etate. In patientes de plus que 65 annos de etate, il es plus probabile que le ovarios es sufficientemente senil pro haber perdite le capacitate de secerner amontas significative de estrogenos in responsa al augmentate activitate gonadotrophic del pituitarios (hormon de stimulation follicular) que es un consequentia regular del administration de cortisona.

Es summarisate le experientias clinic con 30 casos de avantiate cancere mammari tractate durante un periodo cumulative total de 13 annos con 50 a 100 mg de cortisona per die, sequite in multe casos—de accordo con le supra-presentate principios—per administrationes de 15 a 120 mg de thyroide desiccate per die. Sexanta-duo pro cento del patientes exhibiva objective signos clinic o laboratorial de regression del morbo. In 10 patientes isto persisteva durante plus que sex menses. Remissiones prolongate occurreva plus frequentemente in patientes de plus que 60 annos de etate, in patientes in qui ovariectomias habeva essite executate plus que sex menses previemente, e in patientes con hyperplasia cortico-stromal o metastase ovarian. Vinti pro cento del patientes exhibiva reparo ossee, e le therapia thyroide pareva haber un effecto synergistic in al minus tres patientes. Le tractamento a cortisona esseva efficace como ultime recurso e etiam como le initial therapia hormonal de morbo metastatic distante. Le uso simultanee de androgenos o estrogenos con cortisona es contraindicate.

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SERUM GLUTAMIC-OXALACETIC TRANSAMINASE ACTIVITY IN CONDITIONS ASSOCIATED WITH MYOCARDIAL INFARCTION. I. BODILY TRAUMA *

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SERUM glutamic-oxalacetic transaminase (SGO-T) activity was originally demonstrated by LaDue, Wroblewski and Karmen in 1954 to be an aid in establishing the diagnosis of myocardial infarction.[1] This observation has since been confirmed by a number of other investigators.[2-10] Many of these same investigators have also demonstrated the value of the serum transaminase test as an index of liver cell injury.[8-14] In this regard the test has even been shown to be of value epidemiologically in revealing preclinical hepatitis or chronic lingering infection where other liver function studies are not significantly affected.[14] Active rheumatic carditis was also found to produce high levels of transaminase frequently, but these elevations were not consistent and did not reflect closely the clinical course of the disease.[15]

On the other hand, numerous other conditions were shown to be associated with normal values of SGO-T unless acute damage to cardiac, hepatic or striated muscle tissue was involved. These included a wide variety of infectious, neoplastic, degenerative, reactive, allergic and congenital disease states. The normal levels found with pulmonary infarction are of much interest, since pulmonary infarction frequently enters the differential diagnosis of myocardial infarction.[16]

It is well known that glutamic-oxalacetic transaminase (GO-T) is widely distributed in animal tissues, the greatest concentration lying in heart muscle, skeletal muscle, brain, liver and kidney, in decreasing order.[17] Clinicians are cognizant of the fact that a number of these tissues may be damaged in association with myocardial infarction. This damage may occur either as a direct result of the acute cardiac dysfunction, or concomitantly following certain types of injuries known to cause infarction of the myocardium occasionally. It is the purpose of this paper to report on variations in SGO-T activity resulting from trauma, cerebral vascular accidents and right-sided congestive heart failure. These three conditions affect striated muscle, brain and liver, respectively. The manner in which such conditions may be as-

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sociated with myocardial infarction will be discussed in the appropriate sections of this report (I. Bodily Trauma; II. Cerebral Vascular Accidents and Congestive Heart Failure).

Bodily Trauma

The anatomic location and attachments of the heart within the chest cavity place this organ in such a position as to make it susceptible to contusion from sudden decelerating, accelerating or crushing forces. The most frequent cause of such an injury is a compression of the heart between the vertebral column posteriorly and the sternum anteriorly, as may occur when the chest is thrown forward against a steering wheel. Cardiac injury may occur in the absence of a penetrating wound.[18]

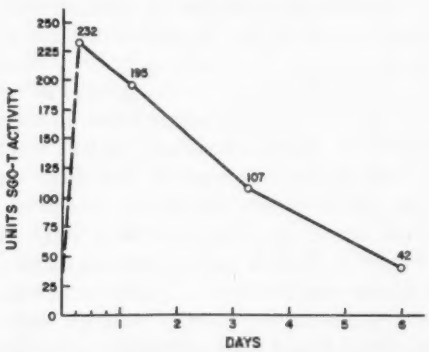

Fig. 1. SGO-T activity in case of trauma with possible heart injury (case 1, table 2).

The cardiac injury may be manifested by electrocardiographic changes indicative of a minor myocardial contusion, a localized area of pericarditis or a myocardial infarction. Cardiac arrhythmias, transient murmurs, fluctuations of blood pressure and even cardiac failure may be associated with cardiac trauma.[19, 20]

Since the determination of SGO-T activity has been shown to be of value in the diagnosis of myocardial infarction, it would appear worthwhile to assess its usefulness in the study of the patient with suggestive cardiac symptoms following trauma.

Case Report

Case 1 (Table 2). This 31 year old Caucasian male was admitted to the hospital following an automobile accident in which he was thrown from the car he was driving. He complained of bilateral pleuritic pain and substernal aching. The blood pressure was 90/60 mm. Hg; pulse, 110 per minute. There were multiple abrasions, and the left twelfth rib was fractured. No cardiac abnormalities were noted on physical examination. Serial electrocardiograms, however, showed transient changes insufficient for a diagnosis of myocardial infarction. These changes consisted of flattening of the

T waves in Leads III, aVF and $V_{5, 6}$, and minimal elevation of the ST segment in aVF. By the following day the voltage of the T waves had improved. However, the T wave in Lead V_5 appeared spiked, an abnormality which disappeared within four days. The SGO-T was studied concurrently and showed the curve demonstrated in figure 1.

The association of SGO-T levels typical of myocardial infarction, along with suggestive electrocardiographic changes, would tend to substantiate a diagnosis of myocardial injury. However, the limitations of a diagnosis based on such evidence will be discussed.

Methods and Materials

The patients were admitted to Harbor General Hospital because of injuries received in a variety of accidents. An electrocardiogram was taken and blood drawn for an SGO-T determination immediately upon admission and at frequent intervals thereafter. The SGO-T activity was determined spectrophotometrically * by the method of Karmen.[2]

Table 1

Total number of cases	51
Transaminase normal	14 (27.5%)
Transaminase elevated	37 (72.5%)
Evidence of cardiac injury	9 (17.7%)
No known heart injury	28 (55.0%)
Transaminase elevated following surgery only	4 (7.9%)
Trauma only—no surgery performed	24 (47.1%)

The possible presence of cardiac damage was estimated by means of serial electrocardiograms and clinical signs. The electrocardiograms of all patients believed to have evidence for heart trauma were reviewed by a cardiologist.†

SGO-T was considered to be elevated when activity was over 40 units. Borderline levels between 40 and 50 units were considered to be elevated only when other specimens from the same patient showed activity at least 10 units lower.

Patients were classified (table 1) according to the level of SGO-T activity and evidence for cardiac trauma. In cases of borderline electrocardiographic changes, the patient was placed in the cardiac injury group. A separate division was provided for those patients in whom elevation of SGO-T activity occurred only following surgical procedures needed for the repair of certain fractures.

Results

Fifty-one persons of all ages involved in accidents were studied. There was no elevation of SGO-T activity in 14 (27.5%) of these patients, 10 of whom suffered fractures (two hips, by simple falls in elderly females; two pelves; one patella; one clavicle; two radii, and three basilar skull frac-

* Transaminase determinations performed at Chem-Tech Laboratories, Beverly Hills, California.

† Electrocardiograms were reviewed by Dr. Morley Kert.

tures). Four of the patients having no elevation of SGO-T activity merely sustained lacerations, abrasions, and cerebral concussion without fractures. In two cases of the same group of 14 patients, only a single determination was made 24 hours after the accident; while in seven cases, two specimens were examined during the first three days of hospitalization. It was felt that an insufficient number of specimens was studied in these nine cases to

TABLE 2

Cases with Presumptive Evidence of Cardiac Trauma

Case	History	Evidence for Cardiac Injury	Transaminase Peak
1. E. E. P. 31 yrs. old WM	Auto vs auto—driving. Thrown from car. Fracture 12th left rib	Flattened T waves Leads III, aVF, $V_{5,6}$. Spiked T V_2. Improved in 5 days	232 (6 hours)
2. B. R. 30 yrs. old WF	Fell off second story roof. Unconscious. Fracture of pelvis, hands, ankles and L_5 vertebra. Lacerated bladder	Transient T wave and ST segment changes in posterolateral leads	211 (37½ hours)
3. C. B. B. 23 yrs. old WM	Motorcycle accident. Fracture-dislocation, left ankle. Fracture right clavicle	Subjective dyspnea, mild. Transient systolic murmur. Inverted T waves Leads III, aVF. Occasional premature ventricular beats	110–115 (persisted from 38–100 hours)
4. H. W. D. 60 yrs. old WM	Fell from moving auto. Compound fracture tibia; fracture fibula	Premature auricular beats. Flattening of T waves, and ST depression Leads II, aVF, and over precordium. Variable Q-T interval. Improved over one week's time. Developed incomplete R. B.B.B.	109 (2 hours)
5. R. E. G. 31 yrs. old WM	Auto vs auto—driving. Fracture mandible. Substernal pain	Spiked T waves $V_{2,4}$. Only a single isolated EKG taken	101 (17 hours)
6. W. F. A. 59 yrs. old NM	Auto vs auto—driving. Fracture left 5–8th ribs.	Left ventricular hypertrophy with strain pattern. T waves improved in 8 days	78 (108 hours)
7. E. M. 24 yrs. old WM	Fell from motorcycle. Unconscious. Multiple abrasions of face and laceration left forehead	T waves inverted Leads III, aVF; flattened $V_{5,6}$	78 (19 hours)
8. A. V. 44 yrs. old Mex M	Auto vs auto—driving. Unconscious. Fracture left 11th rib	Transient peaking of T wave V_2	73 (121 hours)
9. L. N. 22 yrs. old WF	Motorcycle vs auto. Fracture left ankle, pelvis; multiple abrasions	Transient inversion T waves Leads II, III, aVF. Sinus tachycardia —140/min.	52 (12 hours) 65 (second peak on 13th day)

exclude the possibility of a delayed elevation of SGO-T. In five patients, adequately studied with three to five well-timed determinations, the SGO-T level was unaffected.

Thirty-seven patients (72.5%) developed elevated SGO-T levels; of these, nine were considered to exhibit evidence of cardiac injury. Such evidence consisted of electrocardiographic changes in all nine patients, and clinical signs and symptoms in one patient. These electrocardiographic changes involved combinations of T wave flattening and inversion, ST segment shifts, transient spiking of the T waves over the precordium [21] and premature auricular and ventricular beats. The one patient (case 3, table 2) with clinical evidence of transient cardiac dysfunction noted dyspnea, and devel-

oped a transient systolic murmur in the fourth intercostal space to the left of the sternum. This murmur disappeared after one week of hospitalization.

Four of the nine patients in the cardiac injury group were involved in automobile accidents while driving, three were riding motorcycles, one fell from a moving car, and one fell from a second-story roof. All patients suffered multiple contusions, and eight had fractures.

The maximal SGO-T levels ranged from 52 to 232 units in these patients. In two cases (cases 6 and 8, table 2) the apparent peak occurred 108 and 121 hours after injury, respectively; the true peak may have been missed, and the descending portion of the SGO-T curve sampled. In one patient (case 3, table 2) a specimen taken 14 hours after the accident showed 58 units of activity; four specimens drawn consecutively over the next four days ranged between 110 and 115 units, while an eleventh-day specimen showed 83 units. There was clinical and electrocardiographic evidence of cardiac dysfunction, as well as a compound fracture-dislocation of the left ankle which required considerable manipulation. The remaining six patients demonstrated maximal SGO-T elevation between six and 38 hours after trauma, while in one of these (case 9, table 2) there was a second rise on the thirteenth day.

Four elderly women who suffered fractured hips following minor falls demonstrated elevations of SGO-T levels only following surgical reduction of the fractures (table 4). One of these patients, with portal cirrhosis, had minimal ascites but no icterus. Her initial SGO-T level was 24 units. On the first postoperative day hepatic coma developed and the SGO-T reached 1,202 units. The patient died two days later. In the other three cases the SGO-T activity rose to 63, 50 and 49 units, respectively, from one to four days after surgery.

Of the 51 patients studied, 24 (47.1%) showed elevated SGO-T activity without having surgical manipulation or evidence of cardiac trauma. Sixteen were involved in automobile or motocycle accidents, three in falls, four were struck by vehicles, and three were beaten with blunt instruments. The most striking elevation of SGO-T activity in this group occurred in a 40 year old Negro male (case 1, table 3) who was severely beaten about the head. This patient died six hours after the injury, and multiple skull fractures with diffuse, severe cerebral contusions were demonstrated at postmortem examination. A single transaminase test showed 515 units of activity. The two next highest SGO-T levels were found in patients who demonstrated injury to specific organs high in GO-T. Case 2 (table 3), with an SGO-T peak of 378 units, sustained a laceration of the right kidney which was demonstrated by intravenous urography. In case 3 (table 3), with an SGO-T peak of 276 units, the tongue was severely macerated, and there was radiologic evidence suggestive of splenic laceration. The remaining 21 patients demonstrated SGO-T peaks ranging from 43 to 189 units.

In most instances elevation of SGO-T activity developed shortly after

injury. Maximal activity in 17 patients (70.8%) was demonstrated within two days after trauma. In seven patients (29.2%) the SGO-T activity rose gradually, reaching a peak in from three to six days. Two of the latter patients, however, also demonstrated a lesser peak elevation of SGO-T during the first two days after trauma (cases 9 and 11, table 3).

The type of injury sustained by the patients with elevated SGO-T activity was extremely variable and followed no set pattern. Fractures involved skull, ribs, femur, humerus, ankle, hip, pelvis, nasal bone, clavicle and jaw. It was noteworthy, however, that in all patients who sustained fractures of the shafts of any large long bone, such as the femur or humerus, elevation of SGO-T activity was invariably found. All patients had multiple contusions and abrasions.

TABLE 3

Trauma Cases—SGO-T Elevated—No Known Heart Injury

Case	History	Transaminase Peak	Specific Organ Injury
1. C. G. 40 yrs. old NM	Beaten severely about the head, head deformed and bleeding both ears. Died few hours after admission	515 (8 hours)	Severe contusions of brain (confirmed by post-mortem exam.)
2. J. J. 19 yrs. old NM	Driving auto—turned over. Fracture right 9–10th ribs. Multiple abrasions. Gross hematuria	378 (10½ hours)	Kidney laceration visualized on I.V.P.
3. M. C. 36 yrs. old WM	Fell onto rocks while fishing. Severe laceration and contusions of tongue and mouth. Fracture left 12th rib. Possible splenic hematoma noted on x-ray	276 (41½ hours)	Tongue. Spleen ? (x-ray)
4. J. V. 29 yrs. old WF	Auto vs auto—sleeping in front seat. Facial lacerations. Lacerated right eyeball. Left pneumothorax. Fracture of ribs on left. Cerebral concussion	189 (8 hours)	None apparent
5. L. S. 26 yrs. old WM	Auto vs auto. Fracture left femur. Abrasion left cheek. Cerebral concussion	189 (28 hours)	None apparent
6. M. B. 22 yrs. old NF	On motorcycle—struck by car. Multiple abrasions. Basal skull fracture. Laceration right thumb	168 (9½ hours)	None apparent
7. S. W. 30 yrs. old WM	Auto vs telephone pole. Fracture-dislocation left ankle. Dislocation head of left radius. Scalp laceration	131 (60 hours)	None apparent
8. A. B. 34 yrs. old WM	Auto vs pedestrian. Supracondylar fracture right humerus. Multiple abrasions; skin avulsion right lower leg	130 (78 hours)	None apparent
9. A. J. M. 40 yrs. old WM	Auto vs auto. Fracture left femur. Cerebral concussion	66 (39 hours) 128 (5 days—second peak)	None apparent
10. R. H. V. 31 yrs. old WM	Auto vs auto—in back seat. Fracture right femur. Laceration scalp and forehead. Cerebral concussion	100 (9½ hours)	None apparent
11. C. W. P. 65 yrs. old WM	Auto vs auto. Fracture right hip, right ribs, left ischium. Lacerations scalp, arms, left knee, chin and face	43 (12 hours) 93 (5 days—second peak)	None apparent
12. R. H. I. 35 yrs. old WM	Auto vs auto—driving. Cerebral concussion; laceration of face extending into orbit. Fracture nasal bone. Abrasions	83 (30 hours)	None apparent

TABLE 3—*Continued*

Case	History	Transaminase Peak	Specific Organ Injury
13. M. M. 23 yrs. old WM	Auto vs auto—driving. Cerebral concussion. Pain midscapulae. Simple fracture right humerus	74 (45 hours)	None apparent
14. H. D. 21 yrs. old WM	Auto vs auto—driving. Cerebral concussion. Lacerated lip; multiple bruises of right chest wall and face	75 (12 hours)	None apparent
15. E. Z. 80 yrs. old WM	Struck by truck. Fracture 9–10th left ribs. Fracture left tibia and fibula. Large hematoma left flank; laceration left flank and thigh	64 (15 hours)	None apparent
16. L. W. S. 38 yrs. old WM	Fell off electric pole. Fracture right clavicle. Electrical burn middle right finger	63 (6 days)	None apparent
17. M. M. 19 yrs. old WM	Auto vs auto—driving. Cerebral concussion. Laceration scalp and face. Ecchymosis right eye	63 (10½ hours)	None apparent
18. H. C. 35 yrs. old WM	Lost control of motorcycle. Torn ligaments right shoulder. Abrasions	57 (19 hours)	None apparent
19. T. H. 39 yrs. old Mex M	Truck tire blew off on face. Compound depressed skull fracture. Lacerations of face	53 (68 hours)	None apparent
20. W. S. 33 yrs. old WM	Motorcycle vs motorcycle. Fractured skull. Laceration left eye; ecchymosis both eyes. Multiple abrasions	50 (4½ days)	None apparent
21. J. K. G. 50 yrs. old WM	Hit over head with hammer. Unconscious. Fracture jaw. Lacerations and contusions head	49 (11 hours)	None apparent
22. W. B. 29 yrs. old WM	Auto vs truck. Thrown from car. Left pneumothorax. Severe pain left posterior chest	49 (34 hours)	None apparent
23. L. S. 30 yrs. old WF	Fell out of moving car. Basal skull fracture. Few abrasions	44 (33½ hours) (baseline = 33 units)	None apparent
24. M. D. B. 24 yrs. old NM	Auto vs auto—sitting next to driver. Skull fracture. Lacerations face	43 (36 hours) (baseline = 25 units)	None apparent

DISCUSSION

According to these data, elevation of SGO-T activity is likely to occur in an individual subjected to moderate or severe bodily trauma. It is presumed that in the majority of these cases the elevation was not related to cardiac injury, since there was no suggestion of cardiac involvement either clinically or electrocardiographically. *While all of the patients with evidence of cardiac injury showed elevated SGO-T activity, only 24.3% of the patients with elevated SGO-T activity showed evidence of cardiac injury.*

It may be concluded, therefore, that the SGO-T activity cannot be used as a specific test of cardiac injury in accident victims. Patients with cardiac injury uniformly developed elevated transaminase levels, but over 50% of the injured patients tested showed elevation of the SGO-T in the absence of demonstrable cardiac injury.

In injured patients, almost any tissue may contribute to an elevation of SGO-T activity, although the most prominent elevations occurred following injury to a specific organ rich in this enzyme (heart, brain, kidney and

TABLE 4

Trauma Cases—SGO-T Elevated Following Surgery Only

Case	History	Transaminase	
		Baseline	Peak
1. A. J. 74 yrs. old WF	A known cirrhotic. Fell and suffered an intertrochanteric fracture of the right femur. Hip nailed; following surgery developed hepatic coma and died	24	1,202 (1 day postop.)
2. B. B. 89 yrs. old WF	Fell; fractured right hip	30	63 (4 days postop.)
3. A. H. 71 yrs. old WF	Fell; fractured right hip	18	50 (3 days postop.)
4. E. R. 90 yrs. old WF	Fell; fractured right hip	20	49 (1 day postop.)

liver). Injury to a highly muscular organ such as the tongue (case 3, table 3) would be expected to produce a substantial rise in SGO-T, since it is known that striated muscle contains large amounts of GO-T. Apparently contusion and tearing of striated muscle, liberating the enzyme, resulted in most of the observed increases in SGO-T activity. It was noted that every patient with a fracture of the shaft of either the humerus or the femur, both of which are surrounded by large muscle groups, developed a substantial rise in SGO-T activity. Fractures not associated with extensive trauma were not necessarily followed by transaminase elevations.

When the SGO-T activity is plotted against time, two types of curves are distinguishable. Figure 2 illustrates the relationship most frequently observed.

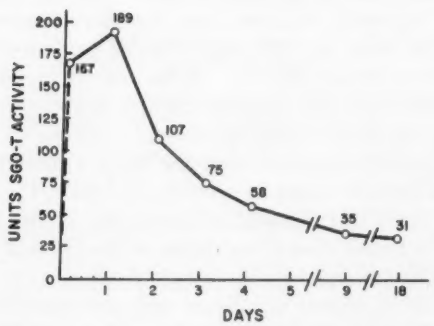

FIG. 2. SGO-T activity in a case of trauma illustrating the early rise of activity (case 5, table 3).

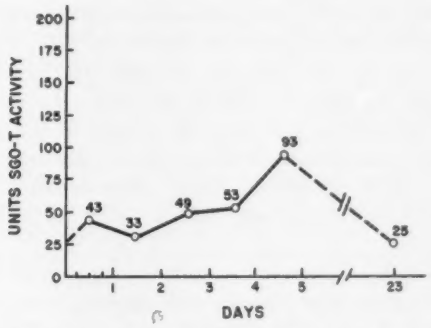

FIG. 3. SGO-T activity in a case of trauma illustrating a delayed second peak of activity (case 2, table 3).

In this case an almost immediate rise in SGO-T activity occurred, presumably due to the immediate injury and liberation of enzyme, and a gradual return to normal levels followed over the ensuing five day period. A curve of this type almost exactly mimics the transaminase curve of myocardial infarction, except for the more immediate rise of enzyme activity seen here.

A second type of relationship is sometimes seen (figure 3).

This case demonstrates a slight elevation of SGO-T occurring shortly after the traumatic episode, and then a more gradual rise, which reached a peak approximately five days later. The early rise presumably represented immediate tissue injury, while the delayed rise of enzyme activity might have been due to subsequent further destruction of tissue. Agress et al. and Nydick et al., in their work on experimental myocardial infarctions,[3, 4] noted a similar second rise occurring in dogs operated upon as controls for their experiments. They explained the initial rise as being due to muscle injury at the time of surgery, while the second rise was attributed to the effects of the anesthetic on the liver. It seems more probable, however, that both

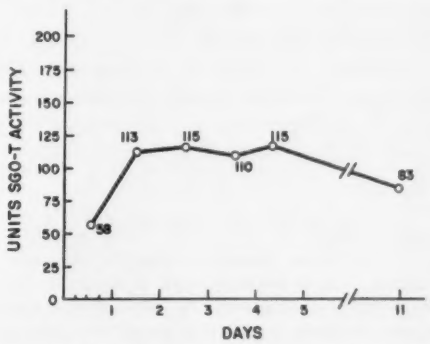

FIG. 4. SGO-T activity in a case of bodily trauma with associated cardiac injury (case 3, table 2).

rises in transaminase activity in our patients resulted from tissue destruction, inasmuch as they were not subjected to anesthesia.

It appears that the patients may be divided into two groups according to the nature of the response of SGO-T activity. In the majority of instances (70.8%) the SGO-T activity rose rapidly to reach its maximal activity within the first two days following trauma, and then returned to normal levels over variable periods of time. In a smaller group (29.2%), transaminase activity rose at a slower rate, to reach its peak activity in three to six days.

A third type of SGO-T curve was seen in one patient who was believed to have sustained cardiac injury along with multiple other injuries (case 3, table 2). This patient was a 23 year old male with no evidence of hepatic disease (normal liver function tests) who had been in exceptionally good health prior to admission. He suffered a compound fracture-dislocation of the left ankle which required repeated manipulation (figure 4).

The SGO-T activity in this case persisted over a period of at least 11 days, although the last specimen examined showed somewhat lower activity. It is possible that the combination of cardiac damage and repeated trauma to the ankle produced the persistent transaminase elevation.

Patients suffering bodily trauma may exhibit serial SGO-T levels closely mimicking those of an acute myocardial infarction. Should such patients undergo simultaneous cardiac injury, the SGO-T test would not be reliable as a differential and diagnostic test. The majority of traumatized patients would probably demonstrate an elevated SGO-T level not of cardiac origin.

Summary

The response of SGO-T activity was studied in patients suffering bodily trauma, since such trauma may predispose to cardiac injury.

Fifty-one patients involved in a variety of accidents were studied with electrocardiograms and serial SGO-T determinations. Although the majority (72.5%) were found to have elevated SGO-T levels, only 17.7% demonstrated additional evidence for cardiac injury; 47.1% revealed elevation of SGO-T activity apparently unrelated to cardiac injury or surgical procedures. It was concluded that SGO-T activity cannot be used as a specific test of cardiac injury in accident victims, since over 50% of the injured patients tested showed elevated SGO-T activity unrelated to demonstrable cardiac injury.

Summario in Interlingua

Le activitate de transaminase glutamic-oxalacetic del sero (T-GOS) esseva studiate in 51 personas con trauma corporee, con le objectivo de establir le valor de determinationes de illo como test diagnostic de infarcimento myocardial in casos de trauma con symptomas que suggere le presentia de un affection cardiac. Le patientes studiate esseva victimas de un varietate de accidentes, admittite al Hospital General Harbor a Torrance in California. Esseva facite un electrocardiogramma e obtenite

specimens de sanguine pro le determination del activitate de T-GOS immediatemente post le admission e a frequente periodos plus tarde. Le activitate de T-GOS esseva determinate spectrophotometricamente.

Nulle elevation del activitate de T-GOS esseva trovate in solmente 14 del patientes studiate (27,5 pro cento). Le presentia de un elevate activitate de T-GOS esseva constatate in 37 patientes (72,5 pro cento). In nove casos (17,7 pro cento), le elevation esseva associate con evidentia de trauma cardiac. In 28 casos (55,0 pro cento), il habeva un elevate activitate de T-GOS sin evidentia de trauma cardiac. In iste ultime gruppo, le maximos del nivello de T-GOS variava inter 43 e 515 unitates. Le plus alte nivellos esseva constatate in casos de trauma specific de organos que se distingue cognoscitemente per alte nivellos de transaminase glutamic-oxalacetic. In le majoritate del casos le elevation de T-GOS esseva explicabile per vulneres de musculo skeletic. Le serie total del patientes se prestava al subdivision in duo gruppos secundo le character del responsa de lor activitate de T-GOS. In le majoritate del casos (70,8 pro cento), le activitate de T-GOS ascendeva rapidemente, attingeva su maximo intra le prime duo dies post le trauma, e retornava subsequentemente a nivellos normal in le curso de variabile periodos de tempore. In le secunde, minus numerose gruppo (29,2 pro cento), le activitate de transaminase ascendeva minus rapidemente e attingeva su maximo intra tres a sex dies.

Super le base de iste datos il pare que un elevation del activitate de T-GOS es probabile in individuos subjicite a un moderate o sever trauma corporee. In le majoritate de iste casos il non esseva possibile supponer que le elevation de T-GOS esseva connectite con trauma cardiac, proque in illos nulle tal trauma esseva manifeste clinica- o electrocardiographicamente. Le conclusion esseva per consequente que le activitate de T-GOS non es usabile como base de un test specific de trauma cardiac in victimas de accidentes.

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SERUM GLUTAMIC-OXALACETIC TRANSAMINASE ACTIVITY IN CONDITIONS ASSOCIATED WITH MYOCARDIAL INFARCTION. II. CEREBRAL VASCULAR ACCIDENTS AND CONGESTIVE HEART FAILURE *

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THE usefulness of the serum glutamic-oxalacetic transaminase (SGO-T) determination was cited in Part I of this report,[1] and the limitations of this test in the evaluation of cardiac injury following accidents were demonstrated. This part will present an evaluation of the SGO-T test in cerebral vascular accidents and right heart failure, conditions that may be accompanied by myocardial infarction, and that involve tissues rich in glutamic-oxalacetic transaminase (GO-T) (brain and liver, respectively).

A. CEREBRAL VASCULAR ACCIDENTS

A cerebral vascular accident may be the presenting and sometimes the only symptom of a coronary occlusion. Bean and Read [2, 3] described eight cases in whom there were symptoms of acute cerebral disease associated with infarction of the heart. A clinical diagnosis of heart disease was not made, however, because the bizarre central nervous system manifestations obscured the picture. It is believed that the cerebral involvement is secondary to the hypotension associated with coronary occlusion. Interestingly enough, actual thrombosis of cerebral blood vessels is rarely found. The neurologic signs are thought to result from reduced cerebral circulation through vessels already narrowed and rigid from sclerosis. The consequent ischemia gives rise to focal signs which are reversible for a limited time. Should the blood pressure remain low, actual infarction occurs and the central nervous disability becomes permanent. Corday, Rothenberg and Putnam [4] describe other situations in which such cerebral damage may occur, namely, hemorrhagic shock, the administration of antihypertensive drugs, postural hypotension, hypersensitivity of the carotid sinus, surgical procedures and anesthetics, sympathectomy, traumatic shock, cardiac arrhythmias and congestive heart failure. They call this entity "cerebral vascular insufficiency."

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Even though myocardial infarction usually presents a well recognized syndrome, complications due to the abnormal physical substratum may camouflage the main disorder. Aware of this fact, the alert clinician is constantly searching to make an accurate diagnosis, since the primary choice of therapy is crucial. Vasopressor drugs may cause complete reversal of cerebral dysfunction secondary to shock of myocardial infarction, but such medication would be contraindicated for the patient with a primary cerebral vascular accident where hemorrhage may be a factor. Of course, it must be kept in mind that a cerebral hemorrhage secondary to anticoagulant therapy, or an embolus arising from a mural thrombus, may also complicate a myocardial infarction.

Case Report

This 81 year old white female was admitted to the hospital after having been found comatose on the floor. On admission she exhibited a left hemiplegia and aphasia. The blood pressure was 110/70 mm. Hg; pulse, 140 per minute. The cerebral spinal fluid was normal; the pressure was 110 mm. water with normal dynamics. The SGO-T activity on admission was 174 units.

During the ensuing five days the patient's condition remained essentially unchanged. The blood pressure fluctuated between 110 and 160 mm. Hg systolic, and 55 to 90 mm. Hg diastolic. Although an electrocardiogram on the day of admission was essentially normal, changes diagnostic of an acute posterior myocardial infarction gradually developed over the subsequent five days. The patient died after three weeks of hospitalization; there was no postmortem examination.

Comment: This case demonstrates the problem of a patient who ostensibly suffered, primarily, a cerebral vascular accident. The normal initial electrocardiogram could only further support this impression. However, suspicion was aroused in the mind of the physician by the fluctuations in blood pressure, and he was finally able to make a correct diagnosis by means of repeated electrocardiograms. The diagnosis was apparently confirmed by the elevated transaminase blood level.

The purpose of this phase of the investigation was to determine what effect a cerebral vascular accident might have on SGO-T activity. This information would be of importance in the differential diagnosis between a primary cerebral vascular accident and cerebral vascular insufficiency secondary to a myocardial infarction.

Methods and Procedure

The patients were admitted to Harbor General Hospital with a clinical diagnosis of recent cerebral vascular accident. The severity of symptoms did not affect the choice of patients. An electrocardiogram was taken at the time of admission and periodically thereafter, depending on the clinical course. SGO-T activity was determined spectrophotometrically * by the

* Transaminase determinations performed at Chem-Tech Laboratories, Beverly Hills, California.

method of Karmen,[5] on specimens drawn daily for from four to six days. Transaminase was considered elevated when activity exceeded 40 units. The patients were then classified (table 1) according to SGO-T elevation and evidence for myocardial infarction.

Results

Twenty-one patients with a diagnosis of recent cerebral vascular accident of varying severity were studied.

In nine cases (43%), studied with an adequate number of determinations, the SGO-T activity remained normal. Of this group, two patients suffered cerebral hemorrhage, and there were seven examples of cerebral thrombosis. The illness was graded as severe in two patients, moderate in two, and mild in five. The severe classification included patients with permanent paralysis frequently resulting in death. Mild cases were those with transient symptoms and good prognosis. The moderate group consisted of patients with persisting paralysis, but apparently good prognosis.

Table 1

Cerebral Vascular Accidents

Total number of cases	21
Transaminase normal	9 (43%)
Transaminase elevated	12 (57%)
Associated myocardial infarction	3 (14.3%)
No evidence for myocardial infarction	9 (43%)

Twelve patients (57%) demonstrated definite elevation of SGO-T activity. In three of these patients electrocardiographic evidence of acute myocardial infarction was found later (as much as one month later in one instance) (table 2, part A), with peak transaminase levels of 188, 174 and 55 units, respectively.

Of the 12 patients with elevated SGO-T activity, nine (43% of the patients studied) were found to have significant elevation with no evidence of cardiac involvement (cerebral hemorrhage, three cases; cerebral thrombosis, six cases) (table 2, part B). The diagnosis in two cases was confirmed by postmortem examination. Eight cases were classified as severe, one as mild. The apparent peak transaminase levels varied from 48 to 100 units. Only a single blood specimen was tested in two of the patients (cases 6 and 9, table 2B), and it was felt that these specimens were not drawn at the optimal time to demonstrate the true peak of SGO-T activity. Another patient (case 5, table 2B) had recurrent cerebral hemorrhages and showed elevations of SGO-T activity six days and six weeks after admission. The remaining six patients had apparent maximal elevations of SGO-T from 24 to 96 hours after the onset of symptoms, although in a few of these who died early it is possible that the greatest elevation of SGO-T was not actually detected. On the average, the highest transaminase levels were found between 48 and 72 hours after the stroke.

Discussion

There was elevation of SGO-T activity in 12 (57%) of the 21 patients with findings of a recent cerebral vascular accident. Three patients (14.3%) were subsequently found actually to have an underlying myocardial infarction, thus illustrating the validity of the statement that the picture of a cerebral vascular accident may be the presenting and sometimes the only manifestation of a coronary occlusion. Elevated SGO-T activity with no demonstrable cardiac involvement was noted in nine (43%) of the cases.

Since brain tissue is rich in GO-T,[6] and since injured tissue releases this enzyme, it seems reasonable to conclude that the elevation of SGO-T activity noted in 43% of the cases was due primarily to the acute cerebral damage.

The SGO-T curve associated with a primary cerebral vascular accident is quite constant, and resembles the curve seen in cases of myocardial infarction (figure 1). The ascending limb of the curve, however, follows a more gradual slope than is usually seen in instances of myocardial infarction (figure 2), and the maximal activity is somewhat delayed. Further studies are indicated to determine the validity of this apparent difference in pattern.

The maximal SGO-T activity is reached approximately 48 to 72 hours following the onset of the illness. The levels found in cerebral vascular accidents do not appear to be so great as those reached in many myocardial infarctions, but such levels of transaminase activity occur frequently enough with myocardial infarction to offer a serious barrier to the interpretation of the test.

Of the 10 patients with severe strokes, eight developed elevated SGO-T activity, whereas elevation was demonstrated in only one patient with mild

Table 2

Cerebral Vascular Accidents—SGO-T Elevated

A. Associated Myocardial Infarction

Case	Presenting Symptoms	Evidence for Cardiac Involvement	Transaminase Peak
1. E. C. C. 86 yrs. old WF	Acute cerebral vascular accident (CVA)—left facial paralysis and left hemiparesis	EKG revealed acute anteroseptal myocardial infarction	188 (4 hours?)
2. A. A. 81 yrs. old WF	Acute CVA—aphasia with left hemiparesis	BP 110/70, P 140 on admission. BP later rose to 160/90. EKG: negative on admission; serial tracings revealed an acute posterior myocardial infarction	174 (24 hours)
3. L. M. 63 yrs. old NM	Acute CVA—left hemiparesis	Initial EKG complicated. Follow up 1 month later demonstrated typical changes of a post-myocardial infarction. Pt. was originally discharged as having a mild CVA. In the 1 mo. interim he had no other symptoms	55 (48 hours)

TABLE 2—*Continued*

B. Primary Cerebral Vascular Accident—No Associated Myocardial Infarction

Case	Diagnosis	Confirmed by	Severity of Symptoms	Transaminase Peak
1. W. H. F. 74 yrs. old WM	Cerebral thrombosis	Clinically. Spinal fluid: Prot 124, Cl 139, Sugar 103, Cells 0	Severe—pt. died. No post mortem	100 (96 hours)
2. G. M. B. 66 yrs. old WM	Cerebral thrombosis	Clinically. Spinal fluid: negative	Severe	83 (72 hours)
3. J. D. 50 yrs. old WM	Cerebral thrombosis	Clinically. Spinal fluid: negative	Moderate—severe	83 (68 hours)
4. R. D. 75 yrs. old WF	Cerebral hemorrhage	Spinal fluid grossly bloody	Severe—pt. died. No post mortem	82 (48 hours)
5. R. N. 70 yrs. old WM	Cerebral hemorrhage	Spinal fluid grossly bloody	Severe—pt. had repeated cerebral hemorrhages, downhill course after 6 wks. of hospitalization	53 (6 days) 75 (6 wks. later)
6. M. M. C. 77 yrs. old WF	Cerebral hemorrhage	Spinal fluid grossly bloody	Severe—pt. died in 24 hrs. No post mortem	68 (10 hours) (1 specimen only)
7. M. P. K. 48 yrs. old WF	Cerebral thrombosis	Clinically	Mild	60 (48 hours)
8. M. A. L. 84 yrs. old WF	Cerebral thrombosis	Post mortem. Clinically	Severe—pt. died	50 (24 hours)
9. K. E. 82 yrs. old WF	Cerebral hemorrhage	Spinal fluid grossly bloody. Post mortem	Severe—pt. died	48 (12 hours) (1 specimen only)

to moderate involvement. Apparently, a mild or transient episode of "cerebral vascular insufficiency" does not cause SGO-T elevation. On the other hand, a clinically *severe* cerebral vascular accident is likely to be associated with a substantial increase. Cerebral hemorrhage and thrombosis were followed by similar degrees of SGO-T elevation.

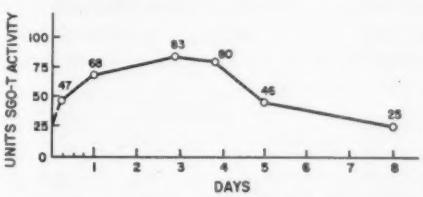

FIG. 1. Case of primary cerebral thrombosis illustrating SGO-T elevation (case 3, table 2B).

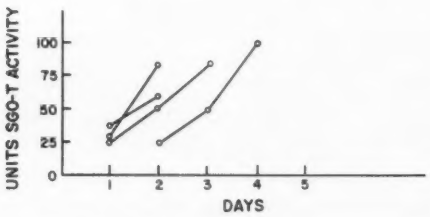

FIG. 2. SGO-T activity in four different patients with cerebral vascular accidents.

B. RIGHT HEART FAILURE

Combined right and left heart failure seldom occurs immediately after an acute myocardial infarction; however, such combined failure may often follow within a few days or weeks.[8] Acute *left* heart failure alone frequently does accompany the onset of an infarction, but theoretically this type of failure should not complicate the use of the SGO-T test. It is in right heart failure that acute congestion of the liver, an organ high in GO-T, may be considered as a possible contributor to the level of SGO-T activity. The need to consider the effect of right heart failure on SGO-T activity is most likely to arise in patients already suffering from congestive heart failure at the time coronary occlusion develops. With this consideration in mind, the evaluation of SGO-T activity in right heart failure was undertaken.

METHODS AND PROCEDURE

The patients were admitted to Harbor General Hospital in moderate to severe right heart failure. A few of the patients were in combined right and left heart failure, but dependent edema and hepatic congestion predominated. Blood for SGO-T activity determination was drawn at the time of hospitalization and at three day intervals thereafter.

RESULTS

Fourteen patients (table 3) in moderate to severe right heart failure with no evidence of acute myocardial infarction were studied. Eleven (78.6%) of these patients showed no elevation of SGO-T activity over 40 units. In this group, however, three patients demonstrated a gradual drop of more than 15 units as compensation was attained. In two cases a drop from 38 to 20 units occurred in three days, while a third patient exhibited a drop in activity from 29 to 23 to 13 units at three day intervals.

TABLE 3

Congestive Heart Failure

Total number of cases	14
Transaminase normal	11 (78.6%)
Transaminase elevated	3 (21.4%)

Three cases (21.4%) demonstrated SGO-T levels above 40 units. In one case an initial 39 units of SGO-T activity dropped to 25 units with compensation, but six days later, after a 37 pound weight loss, the SGO-T activity reached 79 units. No explanation for this delayed rise was apparent. A second patient exhibited 45 units of activity when the congestive failure was most severe, but following a 34 pound weight loss in six days the enzyme level fell to 25 units. A third patient was admitted with an SGO-T level of 420 units, which dropped to 148 and then to 57 units at three day intervals.

Discussion

The majority of patients in moderate to severe right heart failure did not demonstrate elevated SGO-T activity. In a few with initial levels in the so-called normal range, however, there was a gradual lowering of SGO-T activity with the attainment of compensation. Similarly, two patients with definitely elevated initial levels showed a return to normal activity with cardiac compensation.

It would have been helpful to have assessed liver function in these patients. The level of activity in one patient (420 units) actually is highly suggestive of a hepatic etiology. Myocardial infarction rarely elevates the SGO-T activity above 300 units, whereas in acute liver disease such a level is frequently observed. It seems entirely possible that sudden passive congestion of a liver already damaged by chronic heart failure may promote such further damage as to elevate the SGO-T level. Additional studies would be necessary to verify such a hypothesis.

It would appear that right heart failure does not ordinarily affect significantly the level of SGO-T activity, and therefore should not interfere with the interpretation of this test in the evaluation of patients with myocardial infarction.

Summary

The response of SGO-T activity was studied in conditions likely to be associated with myocardial infarction: cerebral vascular accidents and right heart failure.

Of 21 patients with a diagnosis of recent cerebral vascular accident, three had underlying myocardial infarction, and nine showed significant elevation of SGO-T activity with no evidence of cardiac involvement. SGO-T elevation occurred most frequently in cases of *severe* cerebral vascular accident, with curves resembling those of myocardial infarction except for a more gradual initial rise in activity. Hemorrhages and thromboses resulted in approximately equal elevations. It appears that the SGO-T activity determination is of limited value in the diagnosis of myocardial infarction when the picture suggests a severe, primary cerebral vascular accident.

In 11 out of 14 patients with moderate to severe right heart failure, there was no elevation of SGO-T activity, although three of these patients

did demonstrate a gradual drop of over 15 units in their "normal" levels with the attainment of compensation. Three patients demonstrated definite SGO-T elevation which remained unexplained. Right heart failure is only infrequently a complication of myocardial infarction. However, congestion of the liver may have to be considered in evaluating the SGO-T test when symptoms of myocardial infarction appear in patients already in congestive heart failure. Ordinarily, the presence of failure does not interfere with the interpretation of the SGO-T test in individuals with possible myocardial infarction.

Summario in Interlingua

A. Le effecto possibilemente exercite per un accidente cerebro-vascular super le activitate de transaminase glutamic-oxalacetic del sero (T-GOS) esseva studiate in 21 patientes. Proque un accidente cerebro-vascular pote esser le symptoma de presentation e frequentemente representa le sol symptoma in casos de occlusion coronari, information in re ille effecto esserea importante in le evalutation del determination del activitate de T-GOS como base de un test diagnostic.

Le patientes studiate habeva essite admittite al Hospital General Harbor a Torrance in California con diagnoses clinic de recente accidentes cerebro-vascular. Le severitate del symptomas non esseva un factor in le selection del patientes. Al tempore del admission un electrocardiogramma esseva obtenite. Subsequentemente isto esseva repetite a varie intervallos secundo le curso clinic del patientes individual. Le activitate de T-GOS esseva determinate spectrophotometricamente in specimens de obtention diurne durante quatro a sex dies. In le gruppo total de 21 patientes, tres habeva subjacente infarcimentos myocardial, e nove monstrava significative elevationes del activitate de T-GOS (48 a 100 unitates) sin indicios de un affection cardiac. Elevate nivellos del activitate de T-GOS occurreva le plus frequentemente in casos de *sever* accidente cerebro-vascular, con curvas simile a illos trovate in infarcimento myocardial, excepte que le ascension initial del activitate esseva plus gradual. Hemorrhagias e thromboses resultava in approximativemente equal elevationes. Il pare que le determination del activitate de T-GOS es de pauc valor in le diagnose de infarcimento myocardial quando le tableau clinic suggere un sever primari accidente cerebro-vascular.

B. Le studio del activitate de T-GOS in disfallimento dextero-cardiac esseva interprendite pro evalutar le effecto de congestion acute del hepate super le nivellos sanguinee de T-GOS. Le patientes studiate se trovava in moderate o sever disfallimento dextero-cardiac. Un certe numero del patientes esseva in combinate disfallimento dextero- e sinistro-cardiac, sed le dependente edema e congestion hepatic predominava. Sanguine pro le determination del activitate de T-GOS esseva obtenite al tempore del hospitalisation e subsequentemente a intervallos de tres dies.

In 11 ex le serie total de 14 patientes il occurreva nulle elevation del activitate de T-GOS. In tres ex iste 11 casos, il es ver, le effectuation de compensation esseva accompaniate per un reduction gradual de lor nivellos "normal" per plus que 15 unitates. Le remanente tres patientes exhibiva definite elevationes del activitate de T-GOS. Isto remaneva sin explication. Disfallimento dextero-cardiac es un complication de occurrentia infrequente in infarcimento myocardial. Tamen, congestion hepatic es un possibilitate que debe esser prendite in consideration in evalutar le test de T-GOS quando symptomas de infarcimento myocardial appare in patientes qui jam se trova in congestive disfallimento cardiac. Ordinarimente le presentia de disfallimento non obstrue le interpretation del test de T-GOS in individuos con possibile infarcimento myocardial.

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MUCOID IMPACTION OF THE BRONCHI *

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THE existence of dilated bronchi filled with inspissated mucus complicating asthma or obstructive bronchitis has recently been reported. Shaw [1] first described this condition as mucoid impaction of the bronchi. His original paper was presented before the American Association for Thoracic Surgery in 1951 and was published in the *Journal of Thoracic Surgery* in August, 1951. The existence of such a condition associated with asthma or obstructive bronchitis was apparently not then noted by many interested in thoracic disease. Only one report since 1951 mentions the condition and summarizes Shaw's findings in a discussion of bronchiectasis.[2] Because of the lack of such reports, this paper reviews the previous presentation and describes five additional cases.

The underlying cause is not clearly understood, but it is closely associated with asthma or obstructive bronchitis. Undoubtedly many episodes are of short duration and are cleared by the expectoration of plugs of mucoid material. This localized type of inspissated mucus in dilated bronchi may be a result of the same factors responsible for Löffler's syndrome or status asthmaticus. However, it differs from the latter in duration, amount of inspissated mucus and perhaps in location of masses of mucus in the bronchus.

Shaw's pathologic report stated the mucoid impaction of the bronchi resulted from a localized accumulation of inspissated mucus in bronchi of second order, distal to a bifurcation. This was present in the five cases to be reported in this paper. The lung may show areas of irregular, rounded and brown pigmentation on the pleural surface. Examination of the portion involved often reveals soft nodules, the extent of which is difficult to delineate; these are in sharp contrast to the indurated nodules of tuberculosis. In cases with secondary infection, the lesion may be firmer and may show inflammatory changes. In the four cases resected by the author, little reaction was seen on pleural surfaces.

The dissected specimens showed huge bronchi, the largest 2 cm. in diameter. Shaw reported plugs varying from 2.5 to 3.5 cm. in length, and from 0.9 to 2.3 cm. in diameter. The mucus is putty-like and is brown to greenish gray (figures 1 and 2). In some areas peripheral to these masses, viscid clear mucus may be present, or there may be purulent material about the mucus masses, or peripheral to the obstructed bronchi. In some of Shaw's cases, cross-sections through the bronchi showed lamination of the

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plugs of mucus, which was evident in one of the cases of this report, but was not sought in the earlier cases.

Often a microscopic report of granulomatous reaction is made. This is evident from infiltration of lymphocytes, plasma cells, eosinophils, lipophages and occasional foreign body giant cells. Stains of the tissue often show fat-laden lipophages. Sections of other areas of adjacent lung reveal pink staining material in the bronchi, with varying numbers of plasma cells, eo-

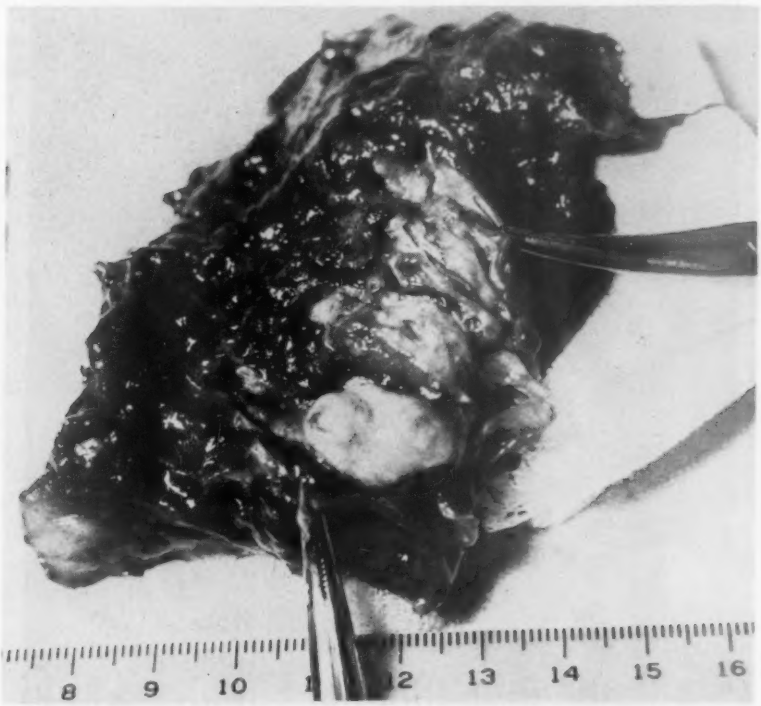

FIG. 1. *Case 3.* The stump of the bronchus is inferior. Three segmental bronchi have been opened longitudinally and show the gross appearance of the inspissated mucus.

sinophils and lymphocytes. In those in which secondary infection has been predominant, acute and chronic inflammation will be evident. Permanent changes in the bronchi often occur, with loss of cartilaginous and smooth muscle elements. The respiratory epithelium may be absent or replaced by squamous epithelium. Sections of lung not involved may show thickened alveolar walls, hypertrophy of the smooth muscle of the bronchi, and varying numbers of eosinophils typical of the microscopic findings of asthma.

Upper lobes were involved in nine of the 10 cases reported by Shaw. In two cases a lower lobe also was involved, and in the remaining case the

middle lobe. All five new cases reported here were in upper lobes, but one also involved the superior division of the lower lobe. This feature of predilection for the upper lobe may be of aid in distinguishing residual bronchiectasis from the usual variety of bronchiectasis, which more often involves the basal segments of the lower lobes.

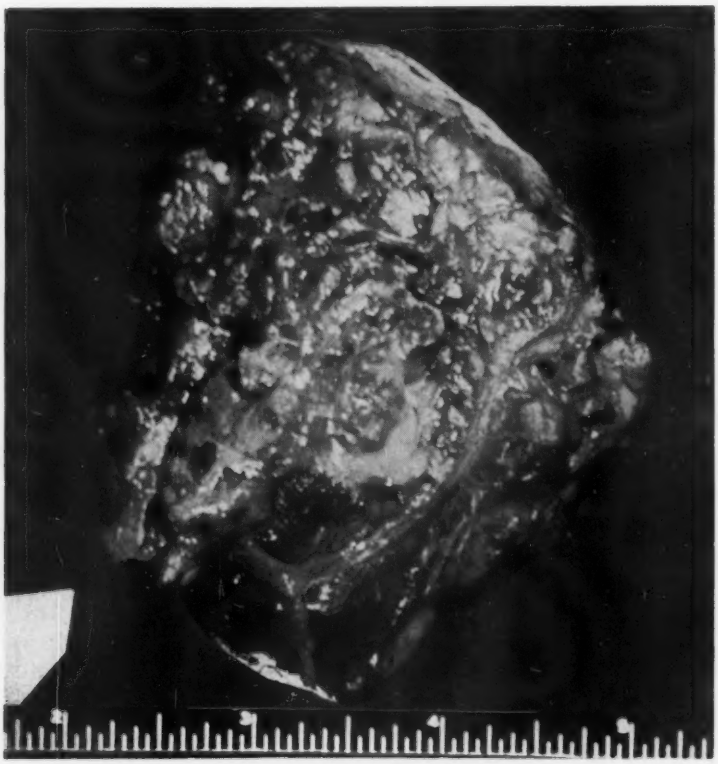

FIG. 2. *Case 4.* The arrow points to the bronchial stump. The mucus mass completely fills the bronchus, which has been opened longitudinally.

Symptoms of mucoid impaction of the bronchi are similar to those of asthma or chronic obstructive bronchitis (wheezing respiration, dyspnea, cough and often a history of allergy). As there may be no new symptoms, the condition may be found by the careful physician taking yearly chest roentgenograms of patients having these chronic diseases. New symptoms may suggest further study. In the reports on 10 cases by Shaw and the five new cases here, several symptoms occurred frequently enough to warrant mention. Fever or a history of pneumonia was present in nine of the 15

cases. Hemoptysis occurred in three cases, chest pain in three, and the expectoration of mucoid plugs in four.

Physical examination is of no aid in the diagnosis, as the findings are those of the underlying asthma, obstructive bronchitis or secondary inflammation.

Roentgenograms show shadows with rather distinctive characteristics. In patients without secondary infection, the plugs cast a V-shaped shadow, with the vertex of the V toward the hilum (figures 6 and 8), or have a "cluster-of-grapes" appearance (figure 3). Atelectasis of varying degree is present in some cases (figure 4). Those with secondary infection show ovoid peripheral shadows reaching the pleural surface. If some of the plugs are expectorated, an air cavity may be evident (figure 12), or an air-fluid level may be seen in an abscess cavity. As the mucus becomes liquefied or as expectoration clears the pneumonitis, the bronchi remain dilated and there are typical findings of bronchiectasis in unusual locations. These may be seen as cystic, mottled areas in plain views (figure 13) and these dilated bronchi are outlined in bronchograms (figure 14). No contrast media enter the bronchi, if the mucus has not been evacuated. The appearance of multiple shadows or other areas with similar findings is also suggestive (figure 9). Planigrams may be of aid in demonstrating the character of the shadow and in viewing bronchi which have been evacuated (figures 6 and 8). The large dilated bronchi which remain may be mistaken for the cavities of tuberculosis.

If a shadow is seen on the chest roentgenogram in a patient with asthma or obstructive bronchitis, the diagnosis is suggested. Symptoms may be fever, pneumonitis, thoracic pain or hemoptysis. Some shadows are evident on chest roentgenograms taken as a routine yearly survey of patients with such chronic pulmonary diseases as asthma. A history of expectoration of plugs of mucus is an important symptom in suggesting the diagnosis.

Treatment may be divided into medical and surgical aspects. Conservative therapy should be followed for these patients, as many have serious impairment of lung function and there may be recurrent episodes.

Medical therapy consists of antibiotics for secondary infection, drugs to relieve bronchospasm, and medication to promote thinning of the secretions to prevent further impaction. Potassium iodide seems to be one of the most effective drugs. Steroid therapy and x-ray therapy do not seem to be of much benefit in this disease. Aerosol Tryptar has been suggested by a colleague interested in allergy, and this might be of some benefit if it could have access to the areas involved. Bronchoscopy is of aid in excluding a visible endobronchial lesion, but it is of no help in evacuating these plugs.

The indications for surgery are the persistence of secondary suppurative disease, persistent hemoptysis from bronchiectasis, and the need to obtain an exact diagnosis. In many patients the differentiation between tuberculosis and mucoid impaction is of much importance from the standpoint of therapy

and loss of time from work. The differentiation between carcinoma and mucoid impaction of the bronchi is even more important, as one wishes to conserve lung tissue in these patients with mucoid impaction. Shaw said gross inspection of the involved lung may be difficult, and differentiation between malignant and benign disease may require opening of the bronchus in question.

A high index of suspicion for the diagnosis of mucoid impaction is necessary to avoid sacrifice of lung where carcinoma is thought to be a possibility. In some patients operation is contraindicated because multiple areas are involved or because of a low pulmonary reserve. As the condition of

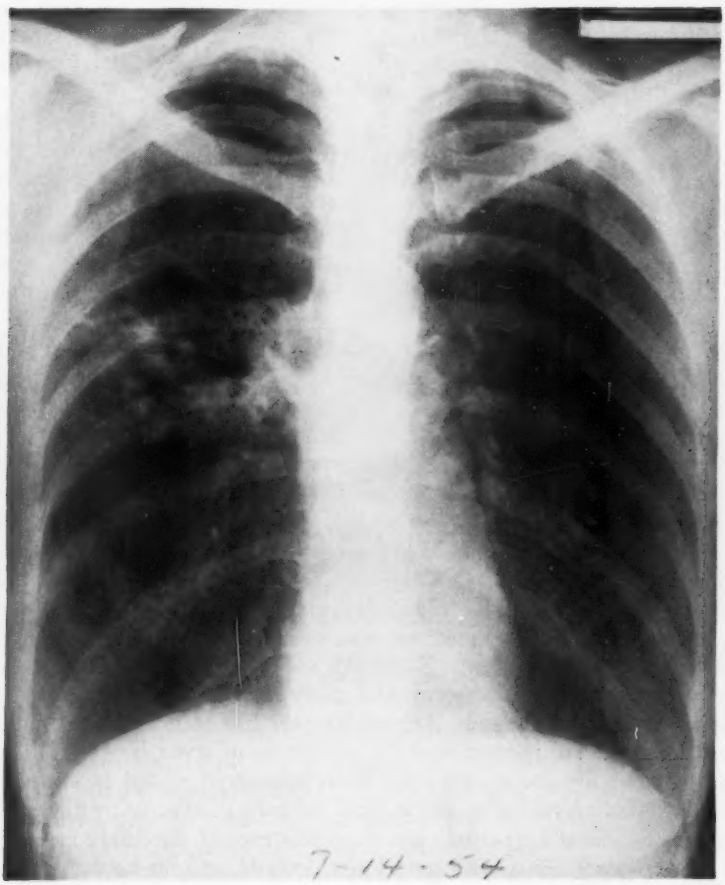

FIG. 3. *Case 1.* Rounded shadows in right midlung field suggested "cluster-of-grape" appearance on PA roentgenogram.

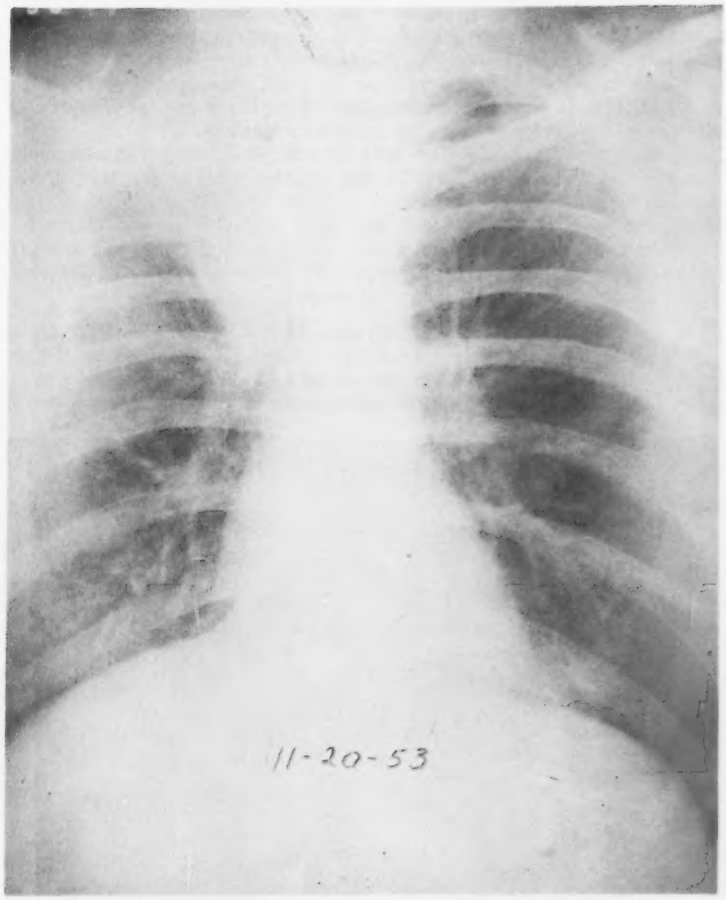

FIG. 4. *Case 2.* PA roentgenogram of chest showed density of atelectasis of right upper lobe of lung.

mucoid impaction becomes generally recognized, fewer errors in diagnosis will be made.

CASE REPORTS

Case 1. A white woman, aged 50, was first seen June 22, 1954. A cough had been present for three or four years and was productive of a small amount of sputum. About six months prior to examination there had been a respiratory infection, with weakness, fatigue and an unknown amount of fever, which was intermittently present thereafter. Vague thoracic pain had been present for two days. Nasal polypi had been removed 18 years before. No history of asthma was elicited.

Physical examination revealed a temperature of 99.2° F. The remainder of the examination was normal.

Roentgenograms on January 26, 1954, revealed a cluster of nodular, rounded and irregular densities in the right midlung field. These remained unchanged on films taken on May 17, 1954, and June 16, 1954 (figure 3).

At the time of bronchoscopy, on June 29, 1954, an aspirated specimen showed normal epithelial cells, and many eosinophils, macrophages and lymphocytes. Three sputum examinations were negative for acid-fast organisms.

Surgical exploration on July 14, 1954, revealed nodular, soft masses in the anterior segment of the right upper lobe and superior segment of right lower lobe. Segmental resections were performed.

Pathologic study revealed findings typical of mucoid impaction of the bronchi.

The patient gained weight and felt very well. Several subsequent examinations revealed occasional sibilant râles. In July, 1955, there was onset of what seemed to be typical asthmatic wheezing, which was treated by her local physician.

Case 2. A white ministerial student, aged 19, had had asthma since the age of two. Mild symptoms had been present for two years, but he was under the periodic care of a physician. Medication was taken most of the time, but the symptoms were not severe and did not interfere with an active school life.

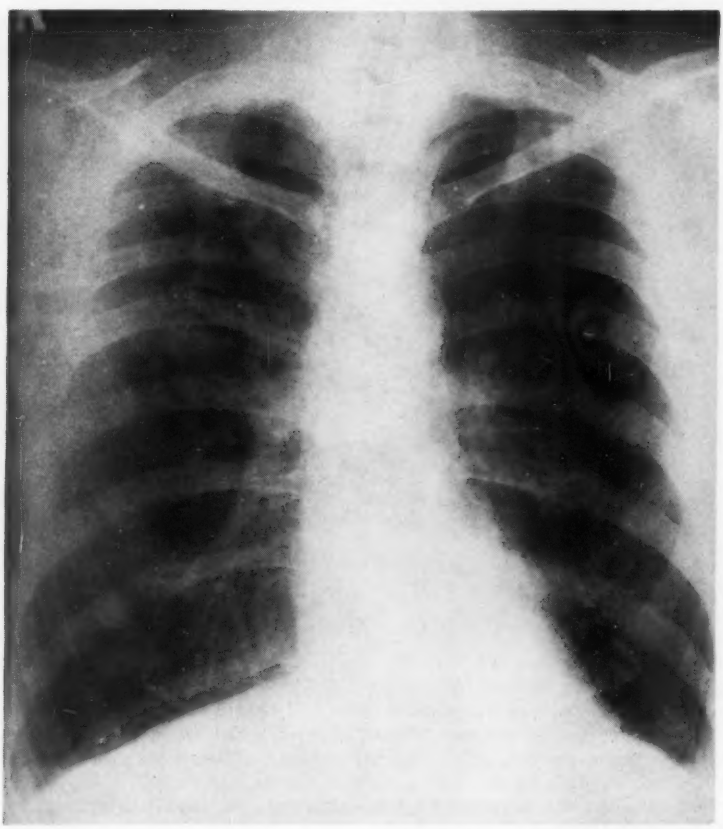

FIG. 5. *Case 3.* PA roentgenogram revealed V-shaped density in right midlung field.

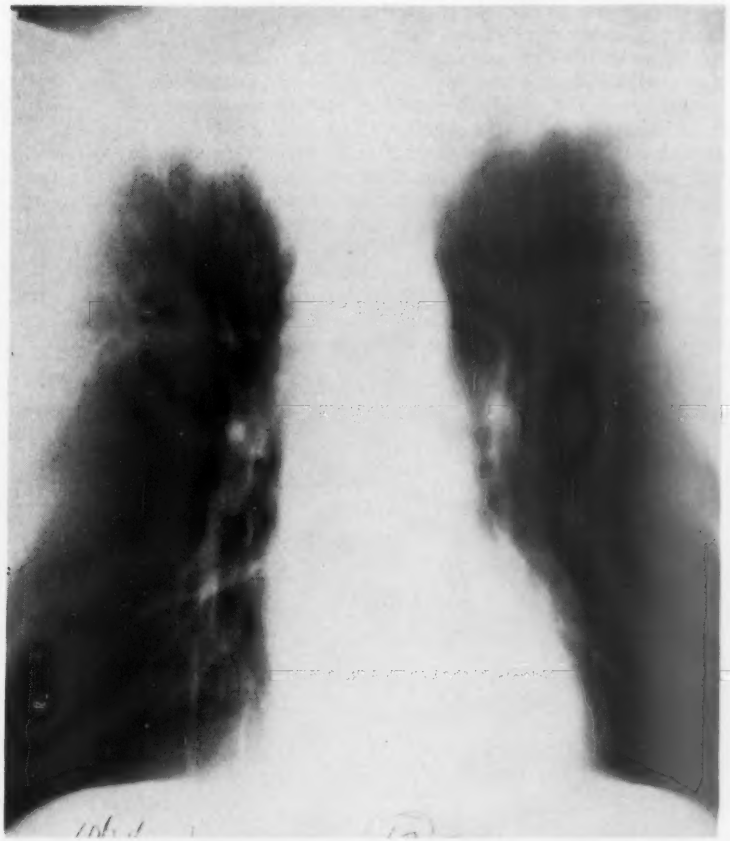

FIG. 6. *Case 3.* Frontal laminagram demonstrated V-shape appearance more clearly.

During a routine examination in November, 1953, an atelectasis of the right upper lobe of the lung was found (figure 4). On November 28, 1953, bronchoscopy was essentially normal. A smear of the bronchus showed a few acid-fast organisms, but cultures were negative for tuberculosis.

On December 28, 1953, a lobectomy of the right upper lobe was performed. The upper lobe was atelectatic, and large, brown, nodular areas were evident beneath the visceral pleura. The bronchi were filled with thick, greenish brown, tenacious material. Many bronchi were markedly dilated, up to 1.3 cm. in diameter. Some of these dilated bronchi reached almost to the pleural surface and seemed to account for the gross appearance on the pleural surface. The microscopic appearance was typical of mucoid impaction of the bronchi.

Convalescence was uneventful, and the patient returned to school two weeks after discharge from the hospital.

Case 3. A white physician, aged 41, who had had asthma since the age of six, required active treatment at intervals. Sibilant râles were usually audible during

routine examinations. The symptoms were easily controlled by medication, and he had carried on an active practice.

A routine chest roentgenogram in May, 1953, revealed a shadow. His physician was consulted, and three gastric lavages revealed acid-fast organisms on direct smear, and one culture of the gastric contents was positive for tuberculosis. He was given I.N.H. and streptomycin for 18 months.

In September, 1953, he had onset of fever which was attributed to superimposed infection, and which responded to penicillin administered parenterally for a short time. During this febrile illness he coughed and expectorated plugs of peculiar tasting, grayish green material. This expectoration of circular and cylindric masses occurred on several occasions during the following months. In March, 1955, he began to have a mild, pleuritic type of pain in the right lateral thoracic region. This varied in degree during the period of observation. In April, 1955, an acute sinusitis occurred, with aggravation of the cough. A few atypical acid-fast organisms were found on smear of sputum, but no positive cultures were obtained. Streptomycin and I.N.H. were again administered.

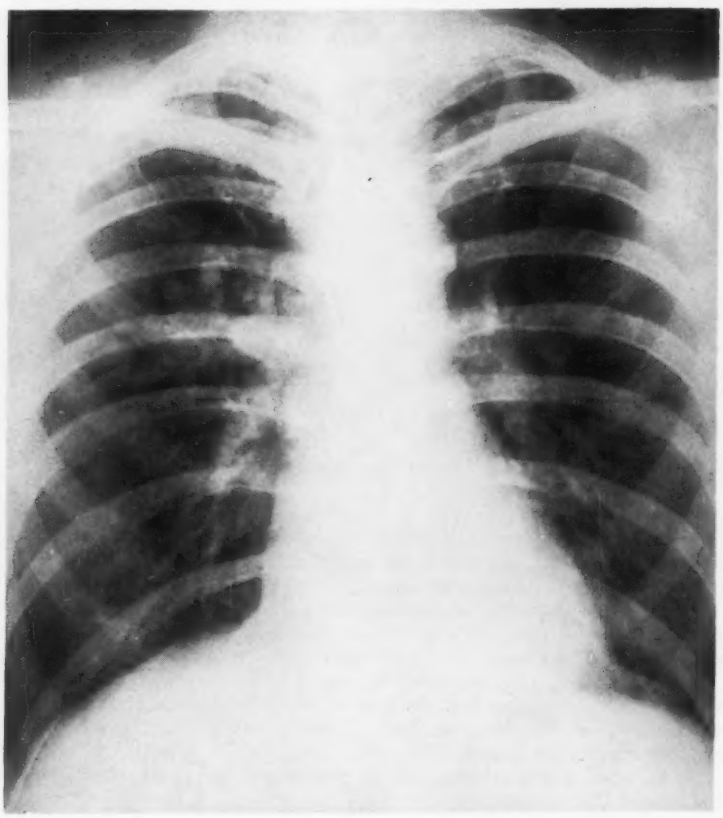

FIG. 7. *Case 4.* V-shaped densities in right upper midlung field were evident on routine roentgenogram.

FIG. 8. *Case 4.* Laminagram revealed club-like shadows of bronchi filled with mucus.

Physical findings were limited to sibilant râles heard bilaterally on occasions.

Roentgenograms revealed a V-shaped density radiating from the upper pole of the right hilar region and some suggestion of a nodular type of density (figure 5), which was most evident on laminagrams (figure 6). Study showed enlargement of the densities, and a second laminagram revealed a rarefied area, suggesting a dilated bronchus or cavity.

On September 15, 1955, a lobectomy of the right upper lobe was performed. Palpation of the lobe revealed a soft, nodular mass with very little suggestion of inflammatory reaction. This involved the posterior segment, which was removed by a segmental resection. The anterior segment was partially involved, and for this reason a lobectomy was done. The apical segment was normal except for a pleural scar. The pathologic report was mucoid impaction of the bronchus (figure 1). No active or healed tuberculosis could be found. Cultures of the lung and mucoid masses in the bronchi were negative for tuberculosis.

The convalescence was uneventful except for an unusual amount of postoperative pain. This gradually subsided and was tolerable after about six weeks.

Case 4. A senior medical student, aged 32, considered himself in good health except for nasal allergy and mild bronchial asthma. These problems had been easily controlled under the direction of a physician for the previous three years. In January, 1954, there was onset of cough productive of mucoid casts of the bronchi. Sputum examinations were negative for acid-fast bacteria. A roentgenogram of the chest was said to be normal.

In April, 1954, the Student Health Service advised BCG immunization because he had a negative skin test for tuberculosis. First and second strength tuberculin tests were done prior to the inoculation with BCG, and both tests were said to be negative. In June, 1954, the tuberculin skin test was recorded as positive. At this time a lesion was first reported on a chest roentgenogram taken for routine examination. He was advised to have a follow-up chest roentgenogram in six months. This

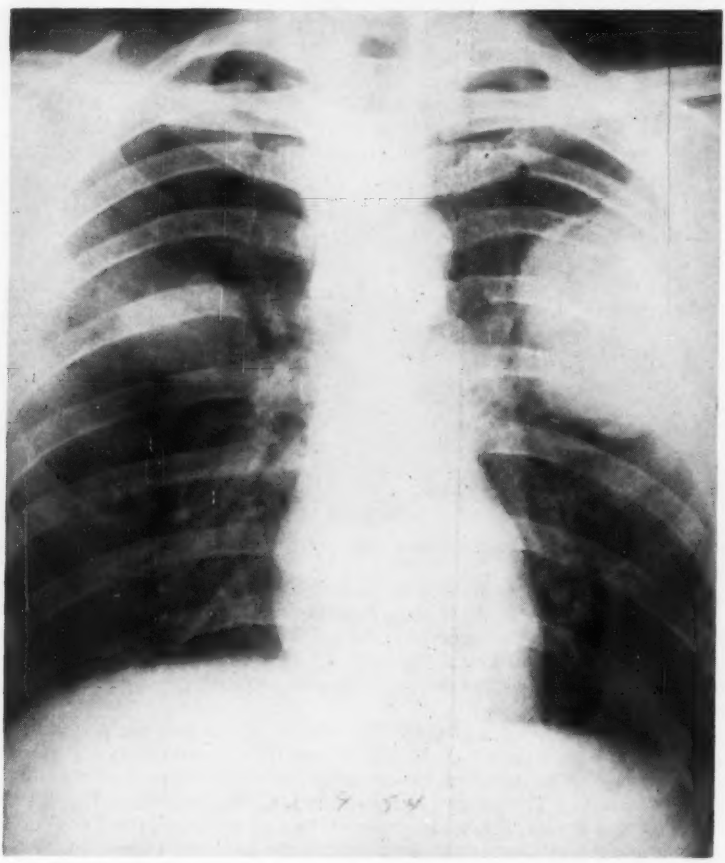

FIG. 9. *Case 5.* Roentgenogram of 12/9/54 showed bilateral symmetric involvement with a fluid level in density on left.

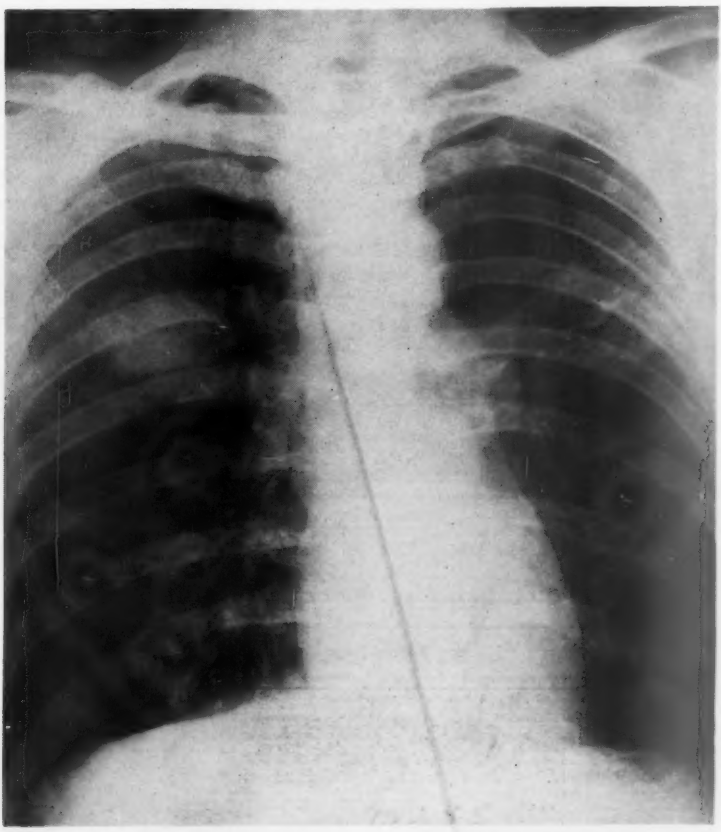

FIG. 10. *Case 5.* Roentgenogram of 1/19/55 showed clearing of densities.

film, taken on December 16, 1954, revealed some increase in size of the shadow in the right upper lobe region.

Physical examination was not remarkable except for fine, post-tussic râles in the right posterior interscapular area.

A review of all roentgenograms (figure 7) showed an area typical of mucoid impaction in the posterior segment of the upper lobe. Even the earlier films were suggestive. Laminagrams were of some aid (figure 8). One small area of involvement in the left lower hilar region cleared after a plug of mucus was expectorated. These lesions were reported by the radiologist as probably inflammatory in origin.

Bronchoscopy revealed no abnormality, and a bronchogram did not reveal any bronchiectasis in the lower lobe. No radiopaque material was visualized in the involved area.

The lesion was thought to be mucoid impaction of the bronchus. However, because the patient had been under observation for an inflammatory lesion, it was necessary to avoid loss of time from school. On January 18, 1955, a posterior segmental resection of the right upper lobe of the lung was performed. The convalescence was

uneventful, and a postoperative roentgenogram months later revealed a satisfactory appearance.

The pathologic diagnosis was bronchiectasis with chronic granulomata which, with the gross appearance, was typical of mucoid impaction of the bronchi (figure 2).

Case 5. A white man, aged 26, had had asthma from early childhood, with a few symptoms after age 15. He became ill in August, 1954, with gradually increasing fatigue, general malaise and loss of weight. These symptoms continued and by November, 1954, he had lost some 25 pounds. Intermittent fever varied up to 103° F. Sputum examination revealed an organism sensitive to Chloromycetin, and this medication was given for several weeks.

Roentgenograms revealed a rounded density in the left upper lung field which subsequently showed fluid levels suggestive of a lung abscess, and a smaller area was evident on the right (figure 9). In January, 1955, he began coughing up chunks of hard material with a rounded, irregular appearance. These varied from BB-shot

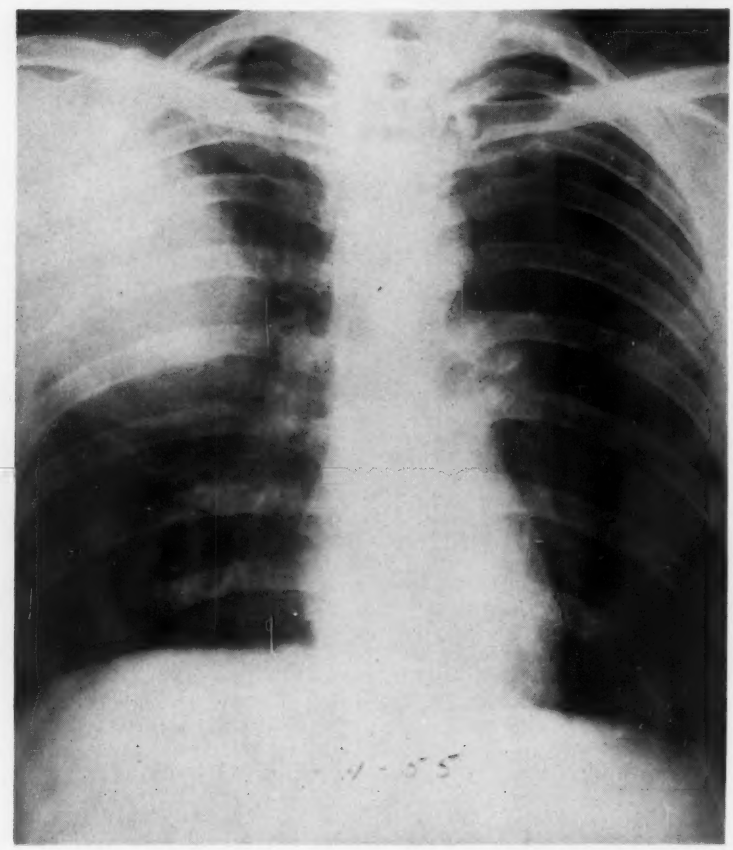

FIG. 11. *Case 5.* Roentgenogram of 3/4/55. Increase in size of shadow in right midlung field, with almost complete clearing on left.

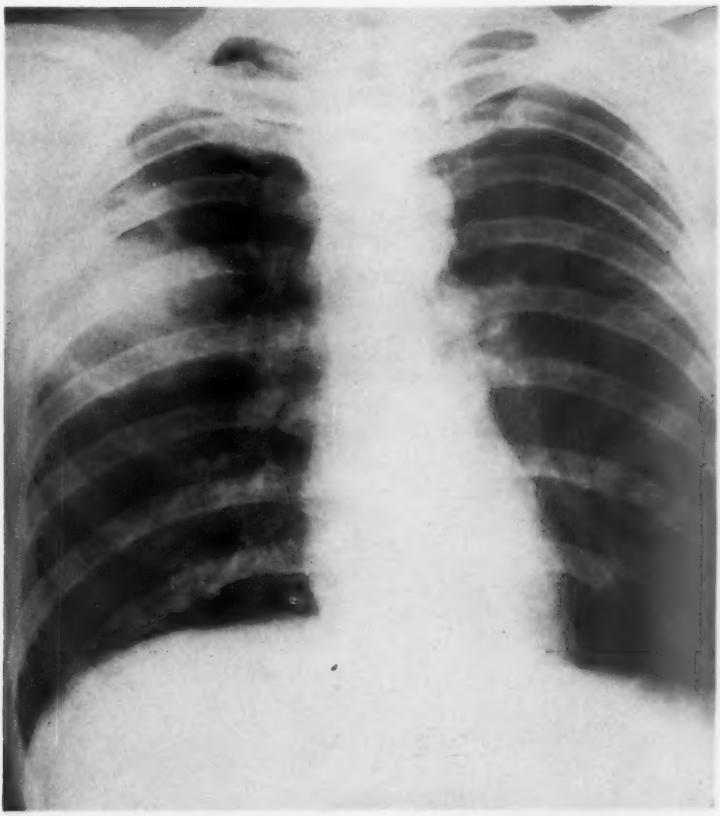

FIG. 12. *Case 5.* Roentgenogram of 4/1/55 revealed appearance of fluid level in shadow of right midlung field.

to bean-sized masses, and had a dark gray color. Roentgenograms revealed clearing of the shadow in the left midlung field but an increase in size and density of the mass on the right, with the subsequent appearance of fluid levels (figures 10, 11 and 12).

He continued to improve and felt quite well despite the changes evident on the roentgenograms. He worked about six weeks and in late February, 1955, had recurrence of fever and other general systemic symptoms. He was hospitalized and again responded to intensive antibiotic therapy. Skin tests were positive for histoplasmosis but were negative for tuberculosis and coccidioidomycosis. He was discharged after about four weeks of therapy. Clearing occurred on the roentgenogram (figure 13).

Two weeks after discharge there was onset of hemoptysis. He was referred to the Chest Clinic, and bronchoscopy and bronchography were performed. The bronchoscopy revealed no source of bleeding. Bronchograms showed bilateral bronchiectasis to be present in the anterior segment of the upper lobes (figure 14).

The patient continued to do well, except for a short febrile bout in September, 1955, which responded to antibiotics. No subsequent attacks of hemoptysis occurred,

but there was some recurrence of asthmatic symptoms that had been mild and were not so severe as those present prior to the age of 15.

Summary

1. The clinical entity of mucoid impaction of the bronchi is reviewed and five additional cases are reported.

2. Roentgenographic findings are rather typical and suggest the diagnosis.

3. Treatment is chiefly medical, but operation may be indicated to verify the diagnosis or to remove lung tissue which has been destroyed.

Acknowledgment

Cases 2 and 3 were studied at the Will Rogers Veterans Administration Hospital, Oklahoma City, Oklahoma. They are reported with the kind permission of C. A. Bates, M.D., Administrator.

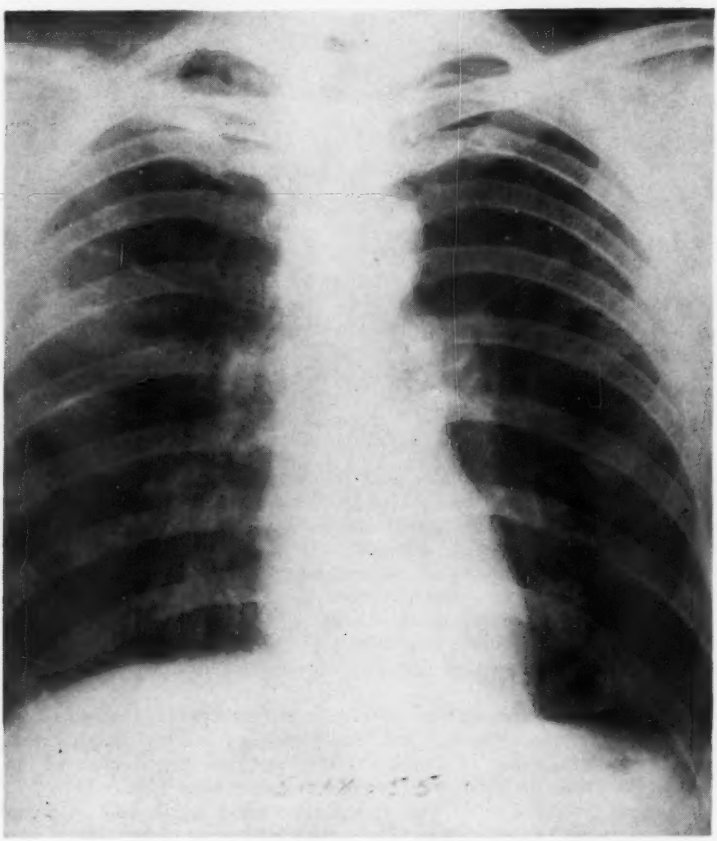

Fig 13. *Case 5.* Roentgenogram of 5/18/55. There was clearing of density in right lung.

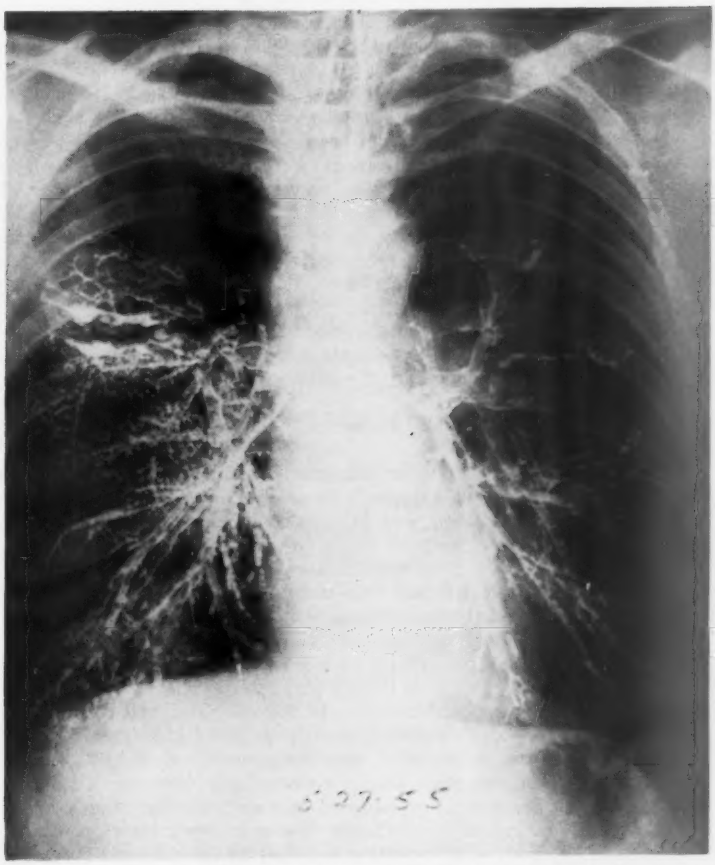

FIG. 14. *Case 5.* Bronchogram (5/27/55) demonstrated bilateral anterior segmental bronchiectasis.

ADDENDUM

Three additional cases have been observed by the author since the paper was submitted for publication. One has cleared on medical treatment and one is under treatment. The third patient had a segmental resection to exclude carcinoma, although the diagnosis of mucoid impaction was suspected. Incidentally, this was the only patient observed with a peripheral blood eosinophilia, varying from 11% to 21%.

SUMMARIO IN INTERLINGUA

Le occurrentia de dilatate bronchos plenate de muco inspissate ha essite reportate per Shaw como complication de asthma o bronchitis obstructive. Le etiologia subjacente non es clarmente comprendite, sed illo es connectite con asthma o bronchitis obstructive.

Le muco inspissate se accumula in bronchos del secunde ordine in sitos distal a bifurcationes. Le examine grossier revela irregular areas brunastre que es molle sub palpation. Un tal area pote inficer se secundarimente e alora exhibir alterationes de morbo inflammatori. Le bronchos es multo grande e plenate de tampons con un variabile longor de inter 2,5 e 3,5 cm e un diametro de inter 0,9 a 2,3 cm. Le muco es del consistentia de mastico e de un color brun o gris verdastre. A vices le tampons es laminate. Periphericamente al tampons, il ha frequentemente muco clar o materia purulente. Le apparentia microscopic pote suggerer un granuloma. Ill es characterisate per un infiltration de lymphocytos, cellulas plasmatic, eosinophilos, lipophagos, e cellulas gigante como corpores alien. Quando un infection secundari ha occurrite, iste alterationes predomina. Un occurrentia frequente es le perdita de elementos cartilaginose e de elementos de musculo lisie. Il pare exister un predilection pro le lobos superior.

Le symptomas es illos de asthma o bronchitis obstructive de longe durantia. Febre, un historia de pneumonia, hemoptysis, e dolores thoracic es symptomas suspiciose. Le expectoration de materia ab le tampons es un symptoma de importantia pro le diagnose.

Le examine physic es sin valor diagnostic. Usualmente illo revela solmente le presentia del asthma subjacente.

Le roentgenogramma monstra un characteristic umbra in le forma de un 'V' con le puncta verso le hilo o un apparentia de un racemo de uvas. In certe casos il pote haber atelectasis. In alteres, con infectiones secundari, le apparentia resimila un abscesso pulmonic. Planigrammas es de adjuta in demonstrar le characteristic densitates de forma de 'V.' Bronchographia es etiam utile in tanto que illo pote monstrar le non-plenation de bronchos ante le expectoration del tampons e plus tarde le alterationes permanente de bronchiectasis.

Le therapia es principalmente medical. Illo consiste de antibioticos contra infectiones secundari, drogas que allevia bronchospasmo, e drogas que promove le resolution del secretiones. Ioduro de kalium pare esser le plus efficace de iste drogas.

Bronchoscopia es utile pro demonstrar le absentia de morbo endobronchial sed non pro evacuar le tampons. Interventiones chirurgic es indicate in casos characterisate per le persistentia de secundari morbo suppurative o de hemoptysis causate per bronchiectasis. Illos pote etiam devenir necessari pro obtener un diagnose exacte. Carcinoma e chronic lesiones granulomatose de natura specific pote esser simulate per iste entiate. Le execution de resectiones debe esser conservatori, proque il existe le possibilitate de altere areas de impaction, e multes de iste patientes possede limitate reservas respiratori. Il occurre casos in que le patientes ha si basse reservas respiratori que le resection es contraindicate.

Es presentate le reportos de cinque casos. In duo le diagnose se suggereva ante le operation. In duo le diagnose non esseva prendite in consideration ante le completion del resection. Le quinte caso esseva tractate medicalmente.

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THE RECOGNITION AND DIFFERENTIAL FEATURES OF INDIRECT REACTING HYPERBILIRUBINEMIA *

By STANLEY REICHMAN, M.D., *New York, N. Y.*, and WILLIAM D. DAVIS, JR., M.D., F.A.C.P., *New Orleans, Louisiana*

INTRODUCTION

THE development of hepatitis in servicemen has been a distinct problem, not only because of the long period of convalescence associated with disability, but also because of the apparent increased frequency in men who return from endemic areas outside the continental United States. For these reasons, as well as to prevent further dissemination, it has been advantageous to set up centers or activities [1-4] to which jaundiced patients may be referred. During the course of treatment of such men, a number of cases have come to the attention of the authors which have mimicked viral hepatitis and, in some instances, had been previously and erroneously diagnosed as acute viral hepatic disease. These patients had been noted either to be jaundiced with or without constitutional symptoms, or had had a recurrence of jaundice after an episode diagnosed in the past as acute hepatitis.

The feature common to all of these patients was a waxing and waning elevation of the indirect fraction of the serum bilirubin and usually normal liver function studies. The subject of this paper is the presentation of these cases in detail and discussion of the causes of this type of clinical picture, with emphasis on the clues which might lead one to suspect that a case of "hepatitis" is actually a rarer condition with a different prognosis.

CASE REPORTS

Case 1. A 19 year old white seaman was admitted to the U. S. Naval Hospital, Portsmouth, Virginia, on December 12, 1955, with the chief complaint of yellow eyes. He had been in the service for about four months and, on questioning, stated that he had noticed yellow eyes intermittently during his entire life. He had no abdominal complaints or fatigability. In October, 1954, he sustained an injury to his left side while playing football, resulting in extreme pain. He was hospitalized for a possible ruptured spleen, but discharged after one week with the doctor's impression that it was a contusion of the spleen. He was told then that the spleen was larger than normal. He had had two transfusions for anemia, but not from blood loss. Family inquiry revealed that a sister also had had an enlarged spleen, which was removed at the age of six for "splenic anemia." The hospital record of that operation was obtained and revealed evidence of abnormal fragility of the red blood cells, and

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From the Medical Service, U. S. Naval Hospital, Portsmouth, Virginia.

The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or of the Naval Service at large.

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TABLE 1

Pertinent Laboratory Data of Reported Cases

Diagnosis	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
	Congenital Hemolytic Anemia		Post-Hepatitis Hyperbilirubinemia	Constitutional Hepatic Dysfunction		
Serum bilirubin (mg. %)						
Weeks 1	2.45	4.27	1.98	4.27	1.47	2.45
2	3.98	1.99	3.31	1.35	1.14	2.57
3	1.56	2.33	2.10	1.88	2.45	0.74
4	—	2.33	2.51	1.14	0.84	2.22
5	2.81	3.06	1.56	0.94	0.36	1.77
6	2.45	3.57	1.77	1.99	1.77	2.45
7	2.57	2.57	1.24	1.45	0.84	—
8	—	3.18	2.22	2.22	1.88	1.45
Months 4	0.44 (postop.)	—	2.10	—	2.33	1.66
6	—	0.55 (postop.)	—	—	—	1.45
8–9	—	—	2.57	1.24	—	0.65
11–12	—	—	1.66	3.44	—	—
Van den Bergh						
1′ Direct	0.27		0.09	0.27	0.09	0.18
Total	3.98		1.34	4.41	1.88	3.71
BSP	N	N	N	N	5.29–4%	4%–11.2%
Cephalin flocculation (48 hrs.)	2+	2+	2+	2+	3+	2+
Thymol turbidity	3.1	1.2	1.7	1.0	5.3	1.2
Alkaline phosphatase	N	N	N	N	—	N
Total protein and A/G	N	N	N	N	N	N
Prothrombin time	N	N	N	N	N	N
RBC fragility	.48–.32%	.44–.28%	—	N	N	N
control patients	.60–.22%	.64–.48%	—	N	N	N
Reticulocytes	2.0%	3.7%	—	N	N	N

complete recovery following splenectomy. Except for an appendectomy in 1953, the patient's past history, social history and family history were essentially negative.

Physical examination revealed a well developed, mildly icteric white male. Blood pressure was 120/70 mm. of Hg. There was a soft systolic murmur over the apex. The liver edge was palpable but was considered within normal limits on percussion. The spleen was palpated 6 to 7 cm. below the left costal margin on inspiration and was quite firm, with a smooth edge. The remainder of the physical examination was negative except for venereal warts.

Pertinent laboratory findings are summarized in table 1. The hemoglobin and

hematocrit were normal. X-ray studies of the gall-bladder revealed numerous radiolucent calculi. A photofluorogram of the chest was negative.

Course in Hospital: This patient was studied for possible hemolysis, because of the history of anemia in the family and the finding of a serum bilirubin which was elevated mainly in the indirect fraction and was accompanied by entirely normal function tests. As indicated, there was an elevation of the reticulocyte count, and fragility studies were distinctly abnormal.

On February 15, 1956, the patient was explored surgically under general anesthesia, and splenectomy and cholecystectomy were carried out. The postoperative course was satisfactory, with prompt healing of the surgical wound and gradual resumption of normal activities. Late in the course of the patient's convalescence, subsequent examinations revealed a drop in the serum bilirubin and gradual improvement in the red cell fragility and anemia. He was seen again on March 28, 1956, at which time he was asymptomatic, afebrile and no longer icteric. He was discharged to full duty.

Comment: This 19 year old man, on close questioning, gave a familial history of "splenic anemia" and a history of icteric sclerae for most of his life. The serum bilirubin was elevated in the indirect fraction, and laboratory studies confirmed the diagnosis of congenital hemolytic anemia. The occurrence of gall-stones was the result of the tremendous turnover of pigment that his gall-bladder was unable to handle satisfactorily.

Case 2. A 19 year old white male had been well and in perfect health until two days prior to admission, when he became more fatigued than usual after playing ball. The following day he noted chills, malaise, headache, and nausea without vomiting. On the morning of admission he became weak while standing and subsequently fainted. He had noted reddish urine that morning, and when seen in the infirmary on August 9, 1955, was found to have icteric sclerae and a large, tender liver. He had not noted any change in the color of his stools, nor had he had any history of exposure to toxic chemicals with the exception of gasoline, which he used to clean his hands. He had never been in the Mediterranean or the Caribbean, and had been in no known contact with jaundiced persons. He had had many immunizations two to four months prior to admission.

The patient's past history was not remarkable except that, on family inquiry, he reported that one paternal cousin had had a splenectomy, and two paternal uncles had had jaundice, probably for their entire lives. All had had attempted splenectomies, but had died after operation. His father had a history of kidney stones.

Physical examination revealed a well developed, well nourished, slender male. Blood pressure was 110/70 mm. of Hg. The head and neck were not remarkable except for mild scleral icterus. The liver was palpated 2 cm. below the costal margin and was nontender. The spleen was not felt on initial examination. The remainder of the physical examination was not remarkable.

Pertinent laboratory findings are summarized in table 1. The hemoglobin averaged 13 gm., and the hematocrit varied between 38 and 44 vol.%. Chest x-ray was negative. A gall-bladder study revealed a functioning gall-bladder with no evidence of stones. Survey of the abdomen revealed scattered gas, and the splenic shadow appeared to be slightly larger than normal.

Course in Hospital: The patient's hospital course was relatively benign in that he became asymptomatic almost immediately after arrival in the hospital. It was first assumed that this patient had infectious hepatitis, but it was soon observed that the serum bilirubin fluctuated considerably—from a high of 4.27 mg.% to a low of 1.99, usually averaging between 2 and 3 mg.%, with elevations almost entirely in the

indirect fraction. Because of these fluctuations in the presence of other normal liver function tests, and a family history of splenectomy, studies to rule out a hemolytic process were instituted. A Coombs' test was reported negative. A blood smear revealed some microcytosis, anisocytosis, macrocytosis and spherocytosis. Reticulocytes were reported at 3.7%. Red blood cell fragility, as noted in the accompanying table, was increased. On October 20, 1955, careful examination of the left upper quadrant was performed and a spleen was definitely palpable. On October 22, 1955, an intrasplenic pressure measurement was performed and found to be within normal limits. On December 7, 1955, the patient underwent a laparotomy, and an enlarged spleen and an accessory spleen were removed. The postoperative course was uneventful, with prompt healing of the surgical wound and gradual improvement in his blood picture. On February 7, 1956, he was reëxamined and was found to be asymptomatic and afebrile, with the wound completely healed. No evidence of continued hemolysis or hyperbilirubinemia was present, and he was discharged to full duty at that time.

Comment: This 19 year old white male was admitted because of an acute gastrointestinal upset. As a result of the presence of icterus, it was presumed that he had infectious hepatitis. In the hospital, splenomegaly was initially missed during his first examinations, but when a fluctuating serum bilirubin was noted, which was elevated mostly in the indirect fraction, accompanied by normal liver function tests, an attempt was made to find another cause for the patient's jaundice. The findings of reticulocytosis, spherocytosis, increased red blood cell fragility and a palpable spleen were diagnostic of hemolytic icterus in this patient. The presence of a positive family history established the familial basis of the illness. It is interesting to note that case 1 was not anemic and case 2 was only mildly anemic.

Case 3. A 23 year old white male was admitted to the hospital on May 5, 1955, for reëvaluation of a diagnosis of chronic hepatitis. He had been initially hospitalized at the U. S. Naval Hospital, Pensacola, Florida, on April 30, 1954. Documentation of this illness was not complete, in that, though he was admitted with an acute febrile episode accompanied by dark urine, the only laboratory tests recorded were those of a mildly elevated icteric index and a normal bromsulphalein retention test after complete convalescence. He was hospitalized for a period of two months in that installation and a diagnosis of acute infectious hepatitis was made. He was admitted to the U. S. Naval Hospital, Portsmouth, Virginia, on August 19, 1954, approximately six weeks after the first hospitalization, because of abdominal pain and itching. The patient stated that about 10 days prior to this second hospitalization he had noted right upper quadrant pain when walking. The pain was sharp in character and radiated along the right lower costal margin. It had been constant for the two days before admission, and was accompanied by some nausea before admission. For seven days prior to admission he had noted some generalized pruritus. He admitted to drinking an occasional alcoholic beverage since previous discharge.

Physical examination revealed a well developed, well nourished white male with no clinical evidence of icterus. Blood pressure was 120/75 mm. of Hg. No abdominal organs were palpable, and the entire physical examination was within normal limits.

Admission laboratory studies revealed a total serum bilirubin of 1.88 mg.%, with a normal thymol turbidity, alkaline phosphatase, cephalin flocculation, and bleeding and clotting times. Urine urobilinogen was positive in dilution of 1:10. Total

serum protein and A/G ratio were normal. Erythrocyte sedimentation rate, hemoglobin, hematocrit and leukocyte count were also normal, and a photofluorogram of the chest was negative.

Course in Hospital: The patient rapidly became asymptomatic during his hospitalization. Laboratory studies revealed that the serum bilirubin varied from 1.14 mg.% to 3.31 mg.%. Repeated bromsulphalein tests were entirely normal. A needle biopsy of the liver performed on August 25, 1954, revealed definite evidence of hepatocellular regeneration with mild condensation of stroma and mild round cell infiltration in both the periportal and intralobular areas. The biopsy was interpreted as repre-

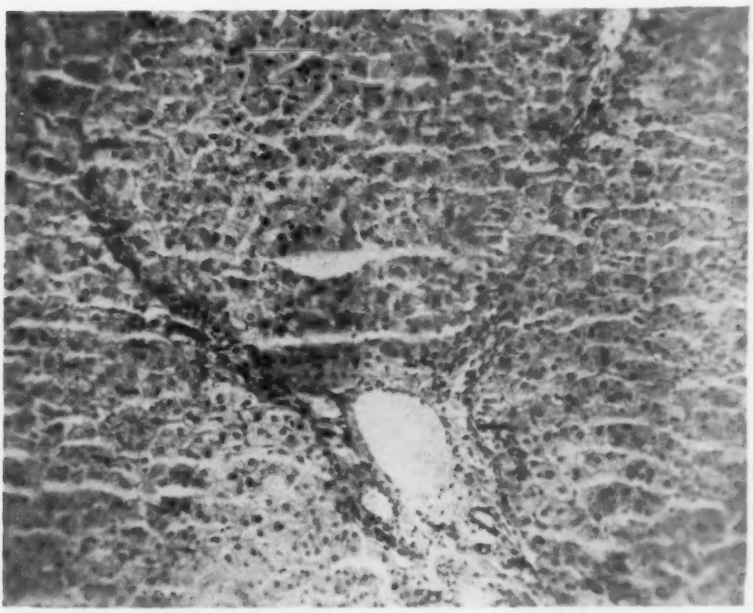

FIG. 1. Liver biopsy in case 3, showing mild periportal inflammatory reaction with evidence of condensation of reticulum extending out into the intralobular areas. These findings are compatible with a diagnosis of previous hepatitis. × 100.

senting mild chronic hepatitis (figure 1). The patient was discharged with a diagnosis of posthepatitis hyperbilirubinemia and given a period of limited duty for six months beginning in November, 1954.

When he was re-admitted for evaluation on May 5, 1955, he was essentially asymptomatic, and admission physical examination was within normal limits.

Laboratory studies are summarized in table 1. A repetition of the liver biopsy revealed evidence of improvement over the previous examination, in that some of the stromal condensation had disappeared. There was residual evidence of regeneration of hepatic tissue and very sparse infiltration of round cells in the intraportal and intralobular areas (figure 2). It was the opinion of the observers that, though this specimen was essentially within normal limits, it was consistent with a previous episode of viral hepatitis. An intrasplenic tissue pressure measurement was performed in this patient and was slightly elevated, being recorded at 180 mm. H_2O,

corrected to 4 cm. retrosternal. The patient remained entirely asymptomatic during his hospital course.

Comment: This 23 year old white male was admitted and studied over a one year period after a poorly documented episode of what was probably acute hepatitis. The absence of abnormal liver function tests, other than the total serum bilirubin, during his initial febrile illness, but the presence of an abnormal liver biopsy recorded during the second hospitalization, appeared to confirm the diagnosis of hepatitis in this patient. Subsequent

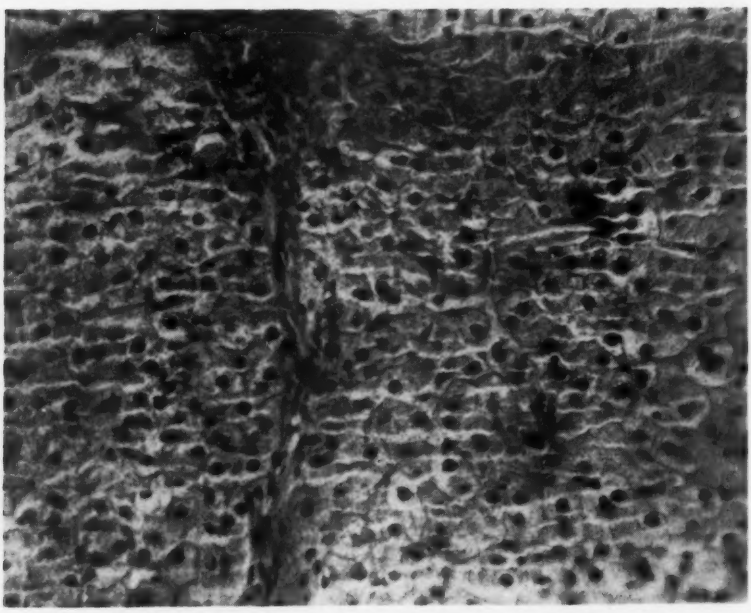

FIG. 2. Liver biopsy in case 3, nine months following the first biopsy. The area portrayed was a maximal area of reticular condensation accompanied by a scattered round cell infiltrate and some hepatic parenchymal regeneration. The over-all picture was that of further healing of the original lesion. × 440.

improvement in all of his tests after the initial episode, with the residual hyperbilirubinemia of indirect fraction lasting over the period of a year, is entirely compatible with the diagnosis of posthepatitis hyperbilirubinemia.

Case 4. A 20 year old white male was admitted to the hospital on February 13, 1955, because of abdominal pain and jaundice. The patient stated that for five years he had been experiencing generalized abdominal cramps, nausea and occasional vomiting of mucus, associated with soft bowel movements and temporary relief of pain following the bowel movements. He had had no blood or mucus in his stools, but complained of considerable tenesmus. The pain was unrelated to food except that, when he had pain, food tended to nauseate him. There was occasional pyrosis. Ten days prior to admission there was mild hematemesis following prolonged retching.

Bowel movements, however, were a normal brown color at that time. For six days prior to the time of admission he complained constantly and had been unable to retain anything by mouth except a small amount of fluid. There was a past history of jaundice three years prior to admission, and he reported that from that time to the present he had had several episodes of yellowness of the eyes. He had also had occasional dark urine and had been treated by his doctor for liver trouble. On February 8, 1955, he noticed that his sclerae were jaundiced, but he felt that by the day of admission they had cleared. The urine was darker than usual at that time. There was also a sensation of coldness, but no chills or definite fever. Some transitory sweating and a sensation of faintness were noted occasionally with the abdominal pain. There had been an estimated 31 pound loss of weight in the few months prior to admission. His past history revealed that he had had jaundice as a child, but no description of this illness was available. It was noteworthy that the patient's father had abdominal pain on occasion.

Physical examination revealed a blood pressure of 138/72 mm. of Hg. There was some discoloration of the sclerae, suggestive of icterus. There was marked tenderness in the epigastrium, but no rebound. The colon was palpable and seemed tender. There was slight hyperresonance to percussion over the entire abdomen and a slight increase in bowel sounds. Feces were a normal soft brown, and the remainder of the physical examination was not remarkable.

Initial laboratory studies included hematocrit, complete blood count, thymol turbidity, alkaline phosphatase, bromsulphalein, serologic reaction, prothrombin time, urinalysis, heterophil agglutination and serum bilirubin. Except for the latter, which was reported initially at 4.3 mg.%, all studies were within normal limits (table 1). X-ray examinations of the chest, thoracic and lumbar spines, gall-bladder and gastrointestinal tract were all normal except for slight scoliosis to the right in the midthoracic region. An intravenous pyelogram was normal. An electrocardiogram was within normal limits, and proctoscopic examination was negative to 25 cm.

Course in Hospital: The patient had recurrent episodes of pain and tenderness in various portions of the abdomen which radiated to the groin but not into the testicles, and was associated with marked prostration and generalized aches and pains. These symptoms were variously relieved by phenobarbital, aspirin, phenacetin, caffeine and reassurance. An interview with the family substantiated an episode of what might have been acute hepatitis in 1952, but also revealed gastrointestinal symptoms throughout his earlier high school period. A careful review of his symptoms indicated a definite relation of some of his symptoms to motion aboard the ship while at sea. Not all of his complaints, however, were due to motion sickness, in that the varying abdominal cramps continued during his hospitalization. The values in the serum bilirubin which seemed to increase with exercise are noted in the accompanying table. It was the opinion of the Service that most of the complaints were the result of functional gastrointestinal disturbance, rather than related in any way to his serum bilirubin, and it was noted that there was no particular relationship between these abdominal complaints and the height of his serum bilirubin. The patient was permitted to return to duty on May 17, 1955, on an antispastic bowel regimen, which resulted in definite improvement of the bowel complaints. It was recommended that, if motion sickness persisted, he be returned for survey from the Navy for that reason.

He was re-admitted five months later, on October 25, 1955, with complaints of episodes of aching in the stomach associated with motion at sea. Most of the complaints were distinctly related to motion sickness, in that they disappeared when the patient was ashore.

Physical examination on this admission was essentially unchanged, and the laboratory studies on admission were again entirely within normal limits, with the exception of the total serum bilirubin, which was 5.33 on admission and varied as

shown in the accompanying table. During this hospital admission a red cell survival time, using radioactive chromate, was within normal limits, and additional studies for hemolytic anemia were negative. A liver biopsy was entirely within normal limits. With the explanation that his illness was unrelated to the jaundice, as well as relief from motion sickness, and with psychiatric help, he gradually became entirely asymptomatic during this admission. Of interest were total hepatic blood flow estimations, determined by utilizing radioactive iodinated serum albumin by a technic to be reported separately,[3] in which portal flow decreased from 1.4 L. to 1.02 L., and hepatic venous oxygen content decreased 1.6 vol.% following exercise.

Comment: Because of the finding of hyperbilirubinemia, a 20 year old white male was admitted to the hospital with abdominal complaints over a five year period resulting from a spastic bowel syndrome and exacerbated by motion sickness. All repeated studies were entirely within normal limits, including biopsy. Because of a history of jaundice that extended into childhood, the absence of hemolysis and lack of proof of previous hepatitis, the diagnosis of constitutional hepatic dysfunction was made. The hepatic vein catheterization studies before and after exercise in this patient revealed a decreased hepatic venous oxygen consumption in the presence of a slowing blood flow. This suggests greater oxygen extraction, rather than a change in utilization, and will be discussed below.

Case 5. A 34 year old white male was admitted to the hospital on January 11, 1956, with the chief complaint of gas pains. He stated that on the previous Thanksgiving Day he had developed a bout of vomiting following an evening of alcoholic indulgence. It was noted on that date that his eyes were yellow and, according to his wife, he had had yellow eyes since that time. On January 7, 1956, he developed another bout of vomiting following another drinking episode, and finally brought up a small amount of bright red blood. He had had hypodermic injections in October and November, 1955, but he had had no known contact with jaundice. He had been a moderate drinker and had previously been jaundiced in 1948, and then subsequently, according to his wife, every time he had even a small amount of beer.

Past history, social history and family history were otherwise noncontributory.

Physical examination revealed slightly jaundiced sclerae. The liver was tender and could be palpated 8 cm. below the right costal margin on deep inspiration. The spleen could not be felt. There were scattered dilated venules over the chest, but no true spiders. Recheck by other observers revealed no hepatic tenderness; the liver was palpated as recorded, but on percussion was not enlarged. The remainder of the physical examination was within normal limits.

Laboratory studies were entirely negative, except for the serum bilirubin, which is shown in table 1. An initial bromsulphalein was recorded at 5% retention, which decreased to less than 4% after hospitalization. An indirect Coombs' test was also positive on two occasions, but no evidence of hemolysis was found in this patient by studies of quantitative fecal urobilinogen excretion, determinations of red cell decay using radioactive chromate, red blood cell fragility, and reticulocyte counts. A liver biopsy was entirely normal. Results of x-ray study of the upper gastrointestinal tract, gall-bladder and chest were normal.

Course in Hospital: The patient became rapidly asymptomatic shortly after his hospitalization, except for periods of anxiety related to marital problems. The change in bromsulphalein and the slightly enlarged liver on admission were considered to be the result of the acute alcoholic bouts that this patient had had prior to his admission. The return of these findings to an entirely normal state within

his first hospital week, the presence of a persistently elevated serum bilirubin without evidence of hemolysis, a normal liver biopsy and no documented history of hepatitis suggested the probability that this patient had a constitutional hepatic dysfunction. It was of interest that whenever the patient was given liberty from the hospital to return home and would exert himself, he would return to the hospital with an elevated serum bilirubin. Intrasplenic pressure measurements performed on this patient were within normal limits. A hepatic blood flow study, using the technic previously mentioned, was essentially within normal limits. During this procedure the patient was given a three minute period of low oxygen breathing, and it was noted that there was a pronounced increase in the total estimated hepatic blood flow.

Comment: A 34 year old male with a moderate alcoholic history had been jaundiced off and on for at least eight years. Study in the hospital revealed an indirect hyperbilirubinemia, with no other abnormalities of his liver function tests and no evidence of hemolysis. A liver biopsy was entirely within normal limits, and it was not possible to implicate chronic alcoholism as the cause of his jaundice. The lack of evidence of hepatitis and hemolysis led to the diagnosis of constitutional hepatic dysfunction by exclusion. The portal blood flow studies are of some interest and will be commented upon below.

Case 6. A 20 year old white male was admitted to the hospital on October 19, 1954, for reëvaluation of a previous diagnosis of chronic hepatitis. Review of his history on this admission revealed that at the time of his original hospital admission he was feeling perfectly well, but that incidental jaundice was noticed by an observant person as he walked down the hall of his installation. He was sent to the hospital on September 23, 1953, with the diagnosis of acute hepatitis. He felt perfectly well for the first four days following hospital admission, and then began to develop some symptoms of general malaise and fatigability. On admission his serum bilirubin was only 1.6 mg.%; the thymol turbidity was perfectly normal; cephalin flocculation test was normal, and the bromsulphalein retention ranged between 5.5 and 7%. During this hospital stay the highest bromsulphalein recorded was 9.6% and the highest serum bilirubin 3.4 mg.%. The patient was discharged to limited duty on April 27, 1954, with a serum bilirubin of 2.2 mg.% and a bromsulphalein retention of 6%. He was essentially asymptomatic except for mild fatigability and malaise. He returned to the hospital in June, 1954, because of general malaise and lassitude, but with no other symptoms. He had been seen as an out-patient and was told that perhaps his condition was due to something more serious than hepatitis. Serum bilirubin, thymol turbidity and cephalin flocculations were done, and when abnormalities were discovered he was again sent back to limited duty. From that time to the above admission he felt well, except for occasional instances of fatigability and "vagueness and dizziness."

Physical examination on this admission revealed a thin, asthenic male who appeared to be in good health. The entire physical examination was within normal limits except for a suggestion of icterus. The liver was palpated 1 to 2 cm. below the right costal margin, but no other organs or masses were palpable in the abdomen, and there was no tenderness.

Laboratory studies on numerous occasions revealed findings which were similar to his initial hospitalization and which are noted in table 1. Serum bilirubins ranged from perfectly normal figures to as high as 3.5 mg.%, the majority of the figures falling between 1.5 and 2.5 mg.% The bromsulphalein retention tests ranged from less than 4% to a high of 12.3%, with the majority around 6% retention. All other

laboratory data were within normal limits. Chest x-ray, barium enema, upper gastrointestinal and gall-bladder films were also normal. Careful studies for evidence of hemolysis were negative. Three separate liver biopsies were performed and all revealed normal liver tissue.

Course in Hospital: The patient complained of fatigue and tiredness on many occasions, but these complaints became less persistent subsequent to a program of physical reconditioning, outdoor exercise and explanation of his illness. He continued to run evidence of clinical icterus on occasion, usually maximal after strenuous exercise, but in view of the repeatedly normal liver biopsies, his initial history (inconsistent with the onset of acute infectious hepatitis), and the benign course of his illness, it became apparent that this patient represented a case of constitutional hepatic dysfunction rather than of acute infectious hepatitis.

Comment: A 20 year old white male had been perfectly well until an observer pointed out that his sclerae were icteric. He was hospitalized with a diagnosis of infectious hepatitis. After study it was noted that, except for a fluctuating serum bilirubin, all the liver function tests were normal, though on occasions the bromsulphalein was elevated. The absence of hemolysis and the presence of repeatedly normal liver biopsies, which militated against a previous episode of hepatitis, soon made it apparent that this was a case of constitutional hepatic dysfunction. The symptoms were iatrogenic in that they developed after hospitalization and disappeared after explanation to the patient of the benign nature of his illness.

Discussion

Elevation of the indirect fraction of the serum bilirubin occurs in the presence of normal liver function either when red cells are destroyed at an excessive rate (hemolysis), or when liver cells are unable to handle normal body pigment metabolism. When the latter is found in the presence of no demonstrable liver disease, it is usually attributed to "hepatic dysfunction" which, on careful study, may be found to be familial in origin. Recently it has been recognized that patients recovering from hepatitis may also show intermittent elevations in the indirect fraction of the serum bilirubin for long periods after recovery from their initial illness.[4] Careful study usually reveals a normal liver profile, and biopsy shows no evidence of active hepatitis. The explanation of the abnormality in both of these instances is obscure.

The cases presented are illustrative of the three categories, i.e., hemolysis, constitutional hepatic dysfunction and posthepatitis hyperbilirubinemia. In all but one instance (case 1) the presence of icterus was thought initially to represent an acute viral hepatitis. In the patients with constitutional hepatic dysfunction, vague abdominal complaints first drew the attention of the medical observer to the patients. In case 4 these complaints initially represented motion sickness. However, when icterus was noted, as in case 6, the subsequent symptoms were iatrogenic in nature, resulting from the patient's anxiety over this discovery of what was thought to represent a

serious illness. Such abdominal complaints, including pain, tenderness in the right upper quadrant, anorexia, and easy fatigability have been reported previously in all of the categories under discussion.[5, 6, 7] It is therefore usual to suspect that those patients who have had a previous hepatitis are progressing to a chronic stage or are undergoing an exacerbation when presenting with this picture. It must be emphasized, however, that the presence of hyperbilirubinemia in posthepatitis patients in the absence of other evidence of disease, as in the patients with constitutional hepatic dysfunction, is distinctly benign in nature, and that treatment or restriction is entirely unwarranted.[5, 6, 7] Explanation of this to patients with symptoms not infrequently results in complete disappearance of all complaints.

The recognition of these entities is important not only for the above reasons, but also because splenectomy may be curative in the hemolytic cases. Although the cases of severe hemolysis are usually easily recognizable, the mild, more chronic congenital forms may be more elusive, occurring both without anemia or demonstrably increased red cell fragility.[8] The vast pigment turnover, with excretion of enormous amounts of bilirubin, not infrequently results in gall-stone formation (case 2). Therefore, the finding of calculi and icterus and normal liver function should not mislead the observer into thinking that he has found the explanation of jaundice within the biliary radicles. A palpable spleen on examination is of no significance by itself, for not infrequently patients with acute hepatitis present this finding with minimal hepatic tenderness or enlargement, but a history of splenectomy in the family (cases 1 and 2) is helpful. In the presence of normal liver function tests, and *prolonged* intermittent hyperbilirubinemia, frequently greatest after exercise or activity,[5, 9] splenomegaly takes on added significance. The absence of anemia, a normal Coombs' test, or a decreased red blood cell fragility after incubation does not rule out hemolysis, though any of these is helpful if present. The reticulocyte count is usually elevated if studied repeatedly; when the bilirubin increases, the total stool urobilinogen rises, and red blood cell survival times are decreased. Finally, evidence of hemolysis in seemingly well members of the family will strongly support the diagnosis.

One of the earliest signs during what appears to be an acute icteric illness —one that should increase the index of suspicion that the patient does not have acute viral hepatitis—is the presence of a normal bromsulphalein test. Bromsulphalein retention in case 6 was misleading early in the course of study, but its fluctuations on continued observation were especially significant. Since many laboratories determine only a total serum bilirubin, or the less valuable icterus index, this finding should immediately alert the physician to request a fractionated bilirubin or a van den Bergh test. An elevated indirect serum bilirubin alone (normal direct < 0.20 mg.%; normal indirect < 1.0 mg.%) does not occur within the first few weeks of a virus hepatitis.

The diagnosis of constitutional hepatic dysfunction or hyperbilirubinemia following acute hepatitis must be made by exclusion. If a familial history is obtainable, then the former may be suspected and more readily diagnosed, provided a careful work-up has been performed and every effort made to rule out hemolysis. In the presence of a normal liver function and normal biopsy, the diagnosis of constitutional hepatic dysfunction may be made in the absence of hemolysis and a history of hepatitis (table 2).

Case 3 seems to be a true posthepatitis hyperbilirubinemia, in that the biopsy findings are available following the acute illness and show healing after the illness subsided despite the persistent hyperbilirubinemia. The importance of liver biopsy in the diagnosis of this syndrome cannot be overemphasized. In any event, prognosis is similar in both of these instances (posthepatitis syndrome and hepatic dysfunction).

TABLE 2

Differential Features of Indirect Hyperbilirubinemia

	Serum Bilirubin	BSP	Splenomegaly	Reticulocytes	Fecal Urobilinogen	RBC Survival	Coombs Test	Family History	G.B. X-Ray	Liver Biopsy
Hemolysis	1′-normal Total ↑	Usually normal	Usually present	↑	↑	↓	May be positive	May be present	May be stones	Normal
Constitutional hepatic dysfunction	1′-normal Total ↑	Usually normal	Absent	Normal	Normal	Normal	Normal	May be present	Normal	Normal
Posthepatitis hyperbilirubinemia	1′-normal Total ↑	Usually normal	Absent	Normal	Normal	Normal	Normal	Absent	Normal	May show evidence of previous hepatitis

This differentiation between constitutional hepatic dysfunction and posthepatitis hyperbilirubinemia may be difficult, and it should be pointed out that a patient having a genuine hepatitis in the past may have had his disease superimposed upon a previously unrecognized constitutional dysfunction. In such a case it would be impossible to differentiate between the posthepatitis syndrome and the constitutional dysfunction. Similarly, a patient suspected of having constitutional dysfunction conceivably could have had a previous bout of hepatitis which was unrecognized and, in the absence of positive biopsy proof, the diagnosis would be impossible unless a family history was present. Parenthetically it should be observed that "carrier states" of viral disease [10] should be investigated in these patients, though generally these "carriers" have additional chemical abnormalities.

The nature of the defect in patients with hepatic dysfunction is unknown. In case 5 there was a pronounced increase in hepatic blood flow, as determined by radioactive technics reported elsewhere,[3] following low oxygen breathing; and in case 4 there was a pronounced decrease in blood flow following exercise, which was accompanied by a fall in hepatic oxygen content.

It is interesting to speculate as to whether hypoxia to liver cells following exercise is of some importance in the production of the hyperbilirubinemia in these patients, since in the cases reported here there was generally increase in the indirect serum bilirubin following increased activity.

This study has not included the recently described syndrome of idiopathic jaundice associated with a lipochrome-like pigment in the liver (Dubin-Johnson syndrome).[11] In this situation, however, the van den Bergh reaction is direct, there is seldom a familial factor, the bromsulphalein test is often abnormal, the gall-bladder is never visualized radiographically, and the biopsy findings are quite distinctive and diagnostic.

Summary

Not infrequently cases are encountered on an active hepatitis ward which superficially resemble viral hepatic disease but which are distinct from it. They are characterized by an indirect van den Bergh reaction and usually normal liver function. This group of patients is comprised of chronic hemolytic disease, constitutional hepatic dysfunction and posthepatitis hyperbilirubinemia. In the former case splenectomy is usually indicated, whereas the two latter are benign and treatment is entirely unwarranted. Experiences with these patients are discussed.

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Summario in Interlingua

Il occurre infrequentemente que on incontra casos de jalnessa que es superficialmente simile a morbo hepatic virusal sed que nonobstante es distincte ab illo. Le ictero es frequentemente recognoscite in le curso de un morbo incidental, e si le ver diagnose non es recognoscite, il pote evenir que le patientes es subjicite a tractamentos innecessari o que le correcte regime es negligite. Iste gruppo de casos consiste de chronic anemia hemolytic, hyperbilirubinemia post-hepatitic, e dysfunction hepatic constitutional.

Le characteristica commun de omne iste patientes es le accrescentia e decrescentia del nivello del fraction a reaction indirecte in le bilirubina seral, usualmente accompaniate per un function hepatic sin ulle anormalitate. In casos correspondente a iste description, il es necessari cercar meticulosemente pro indicios de hemolysis. Si un historia de hepatitis es revelate, un biopsia hepatic deberea esser executate pro determinar le possibile presentia de indicios de un previe episodio de hepatitis. In le absentia de hemolysis o de indicios de hepatitis, on pote formular un diagnose de dysfunction hepatic constitutional. In omne caso, un exacte historia familial pote esser de valor.

Es presentate in detalio sex casos que illustra le aspectos differential de iste syndrome. Duo del casos monstrava signos de un augmento de hemolysis, leve grados de reticulocytosis, e un reducite superviventia del erythrocytos secundo un studio con chromato radioactive. In un del casos, nulle hemolysis esseva constatate, sed un biopsia hepatic revelava indicios de un previe hepatitis. Le remanente tres casos

esseva negative in le respectos mentionate. Illos esseva classificate como casos de dysfunction hepatic constitutional.

Quando le diagnose de chronic anemia hemolytic es establite, splenectomia es possibilemente un mesura curative. In casos de dysfunction hepatic constitutional e de hyperbilirubinemia post-hepatitic, nulle tractamento es indicate.

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A THROMBASTHENIC SYNDROME ASSOCIATED WITH HYPERHEPARINEMIA *

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DEFECTIVE platelet function has been postulated as the basic defect in pseudohemophilia.[17] This is a hereditary hemorrhagic diathesis affecting either sex and characterized by a prolonged bleeding time, normal platelet count and normal clotting time. An intermittent course and spontaneous improvement in later life have been noted. A somewhat similar clinical picture has also been designated as "thrombasthenia" by other authors. Our results in a group of *27* such patients, using more definitive coagulation tests, demonstrated variable platelet dysfunction. Accordingly, we prefer the term "thrombasthenia" for such a syndrome, since it appears more descriptive. All patients demonstrated hyperheparinemia during active bleeding phases, which led to the successful use of protamine sulfate and desoxycorticosterone acetate, as outlined below.

METHODS

1. Total venous platelet counts were done by the Rees-Ecker method. Each recorded count is the average of two pipets and four chamber counts. Our normal values are 200,000 to 400,000 cu. mm.

2. A tourniquet test was done in each case, using a sphygmomanometer cuff inflated to midway between systolic and diastolic pressures for five minutes. A circle, 2.5 cm. in diameter, on the forearm free from large subcutaneous veins was selected for the petechial count. Over 10 petechiae is considered abnormal.

3. The bleeding time was performed by Duke's method on the ear lobe. The normal time is one to three minutes.

4. The oil clot retraction time of Hirschboek [2] was used to measure the rate of clot retraction. This consists of suspending a drop of blood at a castor oil-air interphase and timing the appearance of a pimple of serum on the blood. At 22 to 25° C., our normal time is 24 to 45 minutes. If the

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clotting time and hematocrit are within reasonably normal limits, this test may be used to evaluate platelet function.

5. Serum prothrombin times were done using a one-stage method and bovine fibrinogen (8 mg./ml.) to give a visible end-point. Our normal time is over 30 seconds after one hour post-clotting.

6. Adhesive platelets were computed by the method of Moolten and Vroman.[3] Normal values in our laboratory are 50,000 to 90,000 cu. mm.

7. A modification of Allen's method[4] was used for heparin titrations. Five milliliters of blood were added to 2,000 gamma heparin (Abbott). One-half milliliter of the mixture was added to each of 10 tubes containing 80 to 260 gamma protamine sulfate in 20 gamma increments. The tubes were left undisturbed for two hours, and the end-point consisted of the lowest tube showing a solid clot. Normally, human blood clots in the 100 or 120 gamma tube. In 24 of the 27 patients, this method was checked against LeRoy's method[5] of heparin titration and a photometric method of plasma heparin assay.[6] All three methods agree within 1 gamma. Our normal values by all three methods in 53 normal controls are less than 3.25 gamma of heparin per milliliter of plasma.

8. Clotting times (Lee-White method), one-stage prothrombin times (Quick) and Ac globulin determinations (Stefanini[7]) were performed in all patients. Since all results were within normal values, they are not reported in detail below.

Results of Diagnostic Tests

The results of the various tests in a group of 27 patients presenting a thrombasthenic syndrome are shown in table 1.

This syndrome affected both sexes, 18 being females and nine males. Seven patients showed a familial history of abnormal bleeding. Of particular interest are the two patients with asymptomatic chronic lymphatic leukemia who were not thrombocytopenic and who had shown no previous abnormal bleeding tendency. Since only three similar bleeding problems have been reported in the Negro,[8, 9] it is of interest to note that cases 3, 8, 15 and 17 were Negroes. In all patients, bleeding was confined to the skin and mucous membranes.

At the time of testing, all patients were having active hemorrhagic manifestations except cases 3, 4, 11 and 17, who were symptom-free. All patients demonstrated an abnormal oil clot retraction time and high residual one-stage prothrombin activity in the serum one hour after clotting had occurred in the presence of a normal total venous platelet count and a normal clotting time (table 2). The heparin titer was elevated only in those patients with active bleeding. The bleeding time and tourniquet test were abnormal in the majority of patients. Seven patients showed a low adhesive platelet count, while the remainder were in the low normal range (32

TABLE 1

Patient	Age	R	Sex	Familial	Veno. Plate. (1,000)	Adhes. Plate. (1,000)	Oil Clot Retract. (min.)	Serum Proth. (secs.)	Bleed. Time (min.)	Hep. Titer (g./ml.)	Tour. Test (no pet.)	Active Bleeding
1. R. C.	28	W	F	Yes	308	54	66	26.4	5.5	5.9	22	Skin, nose
2. D. C.	30	W	F	Yes	320	55	53	29.4	1.0	6.4	9	Skin
3. O. M.	42	C	M	No	304	68	59	29.6	1.0	3.9	6	None
4. J. R.	20	W	M	No	282	61	52	24.8	5.5	4.0	25	Nose
5. M. A.	39	W	F	No	254	43	64	22.0	13.0	8.8	33	Skin
6. T. R.	19	W	F	No	325	36	74	18.1	1.5	9.5	64	Skin, uterus, retroperitoneal
7. R. O.	48	W	F	Yes	248	52	60	20.8	14.0	7.2	38	Skin, nose
8. H. C.	26	C	F	No	360	35	88	14.2	42.0	8.8	68	Postop. mastectomy
9. H. M.	26	W	F	No	234	36	105	16.8	21.5	9.6	55	Uterus, nose, gums
10. F. G.	28	W	M	No	300	58	52	23.6	3.0	7.1	29	Bladder, nose
11. L. A.	21	W	M	No	278	62	92	24.0	9.0	3.9	8	Nose
12. H. L.	12	W	F	No	306	54	55	22.8	38.0	7.7	23	Gums, skin
13. S. K.	53	W	F	No	266	44	80	28.0	13.5	6.6	22	Skin
14. F. M.	50	W	F	No	296	56	58	26.6	34.5	7.3	46	Skin, gums
15. G. G.	47	C	M	No	324	60	53	27.7	3.0	8.4	49	Rectum, gums
16. R. D.	42	W	F	No	290	38	108	18.6	29.4	9.2	30	Skin, nose
17. F. H.	40	C	F	No	294	55	66	20.4	2.0	3.8	5	None
18. S. D.	57	W	M	No	208	59	65	19.1	9.5	8.0	17	Postop. tupr.
19. A. G.	58	W	F	No	202	54	60	23.7	2.5	10.8	48	Post-trauma eye
20. K. R.	8	W	F	Yes	285	53	92	20.4	25.0	6.4	54	Skin, eyes, gums
21. S. T.	23	W	F	No	272	56	102	19.6	2.0	7.8	41	Skin, gums
22. S. P.	30	W	F	Yes	264	52	95	20.9	26.5	8.4	3	Nose
23. V. A.	39	W	M	No	236	58	82	23.2	3.0	9.9	58	Skin
24. W. V.	51	W	F	Yes	270	57	96	25.4	2.0	8.0	2	Bladder, rectum
25. P. R.	54	W	M	No	246	60	74	24.3	18.5	7.2	34	Skin
26. S. V.	46	W	F	No	252	59	90	22.0	3.0	9.4	27	Skin, gums
27. D. M.	47	W	M	Yes	268	54	84	21.7	17.0	7.5	32	Nose

normal controls showed an average of 78,000 adhesive platelets, with extreme ranges of 50,000 to 90,000).

An important aspect of this syndrome is the marked lability of the tests when these are carried out at intervals in any single patient. Such a patient is shown in figure 1 (case 5). This demonstrates the danger of undertaking surgical procedures at a time when the tests are abnormal. However, surgery can be more safely undertaken when the tests are normal.

RESULTS OF THERAPY

These studies were initiated by the observation of one of us (I. I.) that the empiric use of protamine sulfate intravenously invariably stopped the nosebleeds in case 4. He received a total of 45 injections over a three year period without untoward reaction, and his nosebleeds always subsided in 15 to 20 minutes after the injection. Because of his distant residence, the effect of the injections could not be followed by laboratory tests.

TABLE 2

Analysis of Tests

Examined during active bleeding	23
Clotting time—abnormal	1
Bleeding time—abnormal	16
Tourniquet test—abnormal	20
Adhesive platelets—abnormal	7
Oil clot retraction—abnormal	27
Serum prothrombin time—abnormal	27
Heparin titer—abnormal	23

As shown in table 1, cases 3, 7 and 13 exhibited a mild form of the disorder and required no specific therapy. Cases 1 and 2 showed temporary improvement following the use of fresh blood postoperatively and required no further therapy. Cases 5 and 8 had no hemorrhagic history prior to operation, but then hemorrhage, both local and general, was severe enough to endanger life seriously. Case 8 subsided following a stormy course, which appeared to be little affected by fresh blood transfusions. The tests on case 6 were carried out when the patient was moribund from internal bleeding.

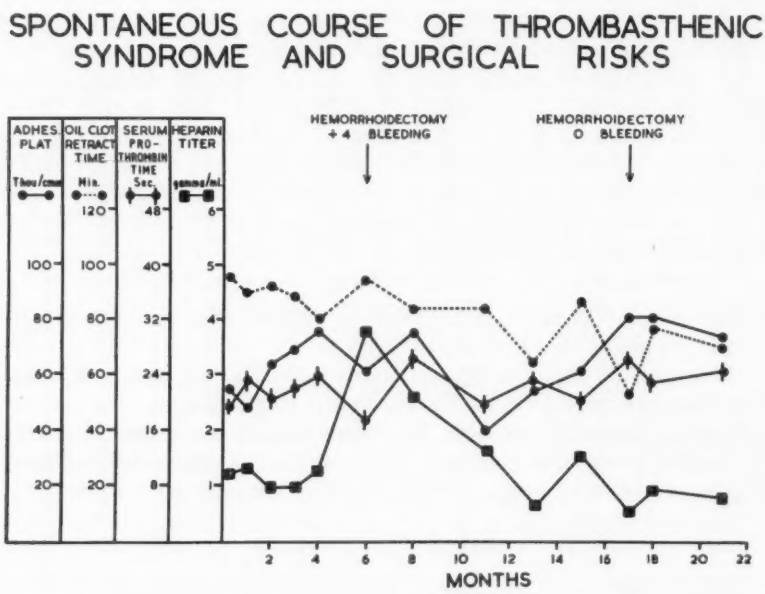

FIG. 1.

The pattern of the abnormal tests in these patients strongly resembled that in a patient previously reported by one of us (W. N. B.).[10] This 42 year old male was thought to have idiopathic hyperheparinemia. The only difference in his case was that his heparin titer was much higher (43 gamma/ml. plasma), and his clotting time was very prolonged (180 minutes). With this possibility in mind, five patients (cases 9, 10, 11, 17 and 18) were given 100 mg. protamine sulfate intravenously. In all cases, the oil clot retraction time returned to normal limits. The heparin titer and serum prothrombin time returned toward normal limits. In one patient (case 11), a subsequent dose of 200 mg. brought the heparin titer and serum prothrombin time to within normal limits.

Case 9 suffered from four to six nosebleeds per week, being most severe in the colder weather. The intravenous use of 100 mg. protamine resulted in prompt cessation of the nosebleeds on each of five occasions. When the injection was given toward the end of a menstrual period, it was noted that the period immediately stopped. On the sixth injection, after 15 mg. had been administered she developed a very severe anaphylactoid reaction which responded to adrenalin and oxygen. Because of our previous finding of benefit in hyperheparinemia from desoxycorticosterone acetate (DCA) [11] (figure 2), this patient was given 6 mg. by linguet therapy daily, with

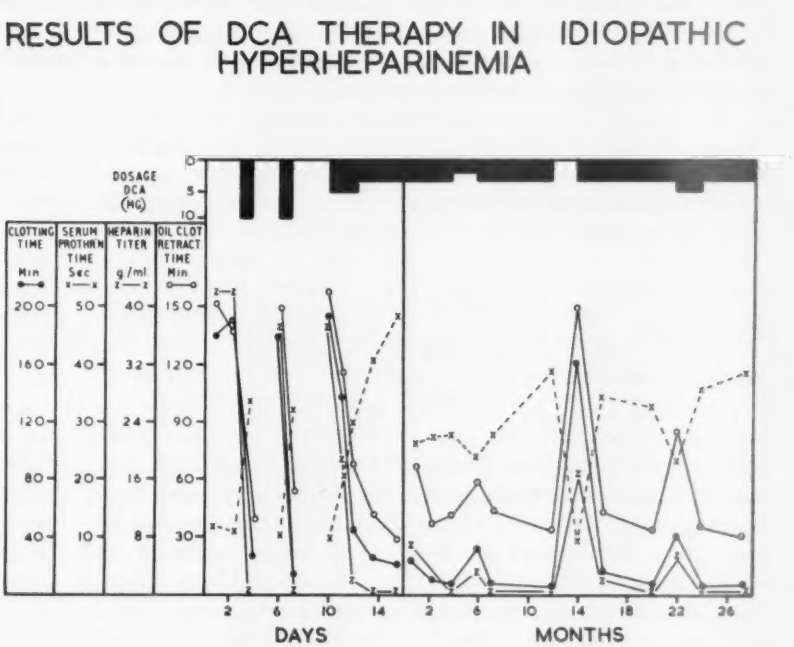

FIG. 2.

gradual reduction to 2 mg. daily. During the ensuing year she had no nosebleeds and markedly reduced menses. She then underwent successful uterine suspension and appendectomy and total dental extraction without undue bleeding.

Cases 18 and 19 had asymptomatic chronic lymphatic leukemia. Case 18 was completely blind in one eye and had a cataract in the other, reducing her visual acuity markedly. When the blunt needle used for anesthesia was introduced subconjunctivally, an immediate large hematoma formed. Although this may happen occasionally in normal individuals, it was felt

that her abnormal coagulation tests were at least a factor. It should be noted that usually in chronic leukemia the oil clot retraction time and serum prothrombin time vary directly with the platelet count. The patient was given 10 mg. DCA intramuscularly daily for two days preoperatively, with 100 mg. protamine intravenously at the start of the operation. Postoperatively she received 50 mg. protamine intramuscularly every six hours, and 10 mg. DCA intramuscularly every third day. Her tests remained normal postoperatively. At no time was any undue hemorrhage noted. Case 19 was studied prior to transurethral prostatectomy. No preoperative therapy was given, but he received 50 mg. protamine intramuscularly every six hours for five days postoperatively. The surgeon reported excess bleeding at the time of surgery, but this stopped with the use of protamine, and further convalescence was uneventful.

All of the patients were followed for from four to 27 months (table 3). Fifteen required surgery during their period of observation. No hemorrhagic complications were observed when the surgery was carried out, either during a spontaneous remission or with protamine and/or DCA therapy.

TABLE 3

Results of Therapy in Thrombasthenic Syndrome

All Patients Followed for from Four to 27 Months

Patients requiring surgery during observation period	15
Hemorrhagic complications during surgery	0
Patients observed without therapy	3
Patients treated by intermittent protamine sulfate or DCA	11
Patients requiring maintenance DCA	13

Eleven patients required intermittent protamine or DCA therapy. Intravenous protamine seemed effective for from six to eight hours, the intramuscular route for from 12 to 15 hours. Intramuscular DCA required from six to eight hours for its effect to become apparent, and the effect would persist for 36 to 48 hours after discontinuation of the drug. Linguet DCA therapy had a latent period of from five to seven days, and its effect persisted for from four to six days after discontinuation. Thirteen patients had hemorrhagic manifestations frequently enough to warrant continual maintenance therapy with DCA linguets. These patients were observed for from nine to 27 months on 2 to 6 mg. DCA. Periodic electrolyte, electrocardiographic and blood pressure determinations were normal.

DISCUSSION

Both vascular and coagulation systems have been incriminated in the pathogenesis of pseudohemophilia. Macfarlane [12] has reported a bizarre pattern and lack of normal contractility of the nail-bed capillaries following traumatic puncture. On the other hand, Glanzmann [1] regarded platelet abnormality as the primary defect in his group of atypical familial bleeders,

and ventured the hypothesis that these presumably abnormal platelets were lacking in an enzyme necessary for normal clotting. The isolated platelets obtained from one of his patients caused coagulation of a platelet-free normal plasma but clot retraction did not occur.

In reviewing the findings in 62 patients with pseudohemophilia, Estren and his associates [13] found a prolonged bleeding time in 100% (often intermittent), a normal clotting time in 95%, and normal platelet counts in 100% of the patients. Clot retraction was normal by the usual tube method in 86% of the patients. As has been pointed out,[14] the rate of clot retraction and the total extent of retraction are probably two different biologic phenomena, so this is not felt to be incompatible with our finding of an abnormally prolonged oil clot retraction time. In fact, good clot retraction in the clotting time tubes was observed in all our patients at four hours. Stefanini [15] has reported normal prothrombin consumption in two cases of pseudohemophilia, but Jurgens [16] found abnormally short serum prothrombin times in 26 bleeders of a family group on the Aland Islands.

We have found that the abnormalities of these tests in these patients tend to be variable and to coincide accurately with their bleeding tendencies. Von Willebrand [17] studied the behavior of platelet suspensions held in a hanging drop of plasma and found ready agglutination occurring in all but the most severely bleeding cases; in these, it was moderately retarded. Our studies with adhesive platelets agree with these findings. It has been shown [14] that there is a direct relationship between the adhesive platelet count and the oil clot retraction time. Our finding that the serum prothrombin time is more seriously impaired than the oil clot retraction time, and that it is not so readily corrected by protamine, suggests that the prothrombin-consumption promoting and clot-retraction promoting qualities of platelets may vary independently of one another. This appears to agree with the findings of Fonio.[18]

The relationship of excess heparinoid activity to pseudohemophilia was reported in a single patient by Castex and Pavlovsky in 1947.[19] This finding is very important, since it suggests suitable therapy for a condition in which therapy has heretofore been unsatisfactory. The only fairly constant benefit reported to date has been from fresh blood (less than 24 hours old). However, this can be of only temporary value. The use of protamine intravenously or intramuscularly offers suitable office therapy, but must be given at frequent intervals to obtain adequate control. Moreover, the occurrence of severe anaphylactoid reactions, as in Case 9, makes such therapy potentially dangerous. The use of DCA by linguet therapy makes easy maintenance control possible. In case of necessary surgical intervention, this may be performed either at a time when the patient's tests have returned spontaneously to normal in elective patients, or after protamine and/or DCA therapy in severe cases, or in case of emergency operations.

Conclusions

1. We have described 27 patients with a thrombasthenic syndrome characterized by a normal clotting time and venous platelet count, low normal adhesive platelet count, prolonged oil clot retraction time, decreased serum prothrombin time, frequently prolonged bleeding time and abnormal tourniquet test. These patients have an increased blood heparin titer during hemorrhagic phases.

2. Females were more commonly affected than males, and all ages may be affected. Both Negro and white patients were affected. The syndrome may show a familial tendency, may occur spontaneously, or may develop in the presence of other disease processes.

3. Protamine sulfate and desoxycorticosterone acetate were found to be valuable therapeutic agents in these patients.

Summario in Interlingua

Esseva constatate in 27 patientes con sanguination cutanee e mucosal un defecto qualitative del plachettas, manifeste in un prolongate tempore de retraction del coagulo secundo le methodo a oleo (de Hirschboek), un reducite tempore de prothrombina seral, un prolongation del tempore de sanguination, positive tests de tourniquet, e basse proportiones de plachettas a adhesivitate normal. Omne le patientes habeva elevate nivellos de heparina del sanguine durante periodos de hemorrhagia active. Ambe sexos esseva afficite. Omne gruppos de etate esseva representate. Sulfato de protamina e acetato de disoxycorticosterona se provava efficace in le therapia de iste patientes. Le secunde de iste drogas, administrate in forma de linguettas, se monstrava particularmente utile como medio de therapia de mantenentia. Dece-cinque del 27 patientes requireva operationes chirurgic durante que illes esseva sub observation. Nulle adverse complicationes hemorrhagic esseva incontrate.

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LABORATORY AND CLINICAL PHARMACODYNAMICS: OBSERVATIONS ON WIN 8778, WIN 12,512–2, AND WIN 13,596–2, AND AN APPROACH TO STUDYING THESE AND SIMILAR ANTIHYPERTENSIVE AGENTS *

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Introduction

Because of the growing number of new agents available for the treatment of hypertensive diseases, the need for simple, efficient and accurate technics for screening these compounds has arisen. The technics should also provide the criteria by which the clinician can determine the efficacy of new antihypertensive agents. We feel that at least three criteria should be fulfilled by any new agent that is to be used for the treatment of hypertension; these are: 1) the drug must be potent in the reduction of abnormally elevated blood pressures; 2) gastrointestinal absorption must be adequate and should be constant so as to achieve uniformity and predictability of results (a high degree of absorption orally is desirable); and 3) the ratio between the hypotensive effect and toxicity should be high.

The technics that we used in the current report for evaluating some new antihypertensive agents have previously been applied to some other antihypertensive agents that we have studied.[1] Preliminary observations are made in our laboratory on dogs in order to evaluate the hypotensive effect, as well as the acute and chronic toxicity with special reference to effect on renal hemodynamics. The site of action of each drug, with reference to the autonomic nervous system, is determined by observing its effect in altering the blood pressure response to stimulation of the distal and proximal ends of the severed vagus nerve, the hypertensive effects associated with carotid occlusion and sympathetic stimulation, and the hypertensive effect of intravenous norepinephrine. When the drug is found to be fairly satisfactory in all of these categories, it is then investigated in detail in a limited number of patients exhibiting hypertensive disease of various etiologies on a controlled "hypertensive ward." When the clinical pharmacodynamics have been evaluated and the drug is found to satisfy the requirements of po-

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tency, adequate absorption when taken orally, and low toxicity, the drug is then taken to the hypertensive out-patient clinic and given to a larger number of ambulatory patients in order to observe its long-term beneficial results in patients with hypertensive disease.

Recently three new drugs have been presented to us for study: Win 8778, an adrenergic blocking agent; Win 12,512-2, a ganglionic blocking agent; and Win 13,596-2, a centrally acting agent with minimal ganglionic blocking activity. Thus, the subject of this paper is the presentation of our technics for the evaluation of new antihypertensive agents, and the application of these technics in studying three new antihypertensive agents. This will be followed by general recommendations concerning the future development of these drugs.

Materials and Methods

A. Win 8778 (Adrenergic Blocking Agent).

1. Laboratory Investigation. The effect of graded doses (0.25, 0.5, 1 and 2 mg./kg.) of 8778 on the pressor response to carotid occlusion, central vagal stimulation, and norepinephrine administered intravenously, was observed in 22 dogs which were anesthetized with pentobarbital (30 mg./kg.).

The renal hemodynamic response to this agent was studied in three groups of dogs receiving increasingly larger doses of the drug. The first group of (four dogs) received 0.5 mg./kg. of the drug; the second group (five dogs) received 1.0 mg./kg.; and the third group (nine dogs) received 2.0 mg./kg. The latter group was largest since these dogs received the dose of the drug (2 mg./kg.) that appeared to produce maximal reduction in blood pressure without undue toxicity. Doses in excess of this amount were tried (4 to 8 mg./kg.) but were found to be toxic, frequently killing the animals. The dose was prepared from the crystalline compound of the drug, and injected immediately after preparation, without autoclaving. Observations were made on glomerular filtration rate, renal plasma flow, renal blood flow, and on the excretion of water and electrolytes as well as on serum electrolyte concentrations.[2] Creatinine was used to measure glomerular filtration rate and para-aminohippurate to measure renal plasma flow. Methods and technics have been described previously.[2]

2. Clinical Investigation. The drug was then evaluated in human patients. There were 10 male patients with hypertensive cardiovascular disease. They were studied in the hospital and maintained on an 800 mg. sodium diet and 3,000 ml. distilled water, and were observed by the frequent recordings of blood pressure in the recumbent and upright positions. The vital statistics of these patients are presented in table 1. The drug was then given as a single oral dose at 10 a.m. on a given morning in an incremental fashion until a significant reduction in blood pressure was observed.

Observations were made on the onset and duration of the effect as well as clinical symptoms which appeared during the reduction in the blood pres-

sure. After the drug had produced a lowered blood pressure, the patients received an intravenous infusion of norepinephrine so that we might observe the effect of this drug on the hypotensive response to Win 8778. The drug was subsequently studied in a smaller group of patients as an intravenous infusion over a short period of time. Two of the patients received 0.5 mg./kg., three received 1.0 mg./kg., and two received 3.0 mg./kg. of the drug.

TABLE 1

Vital Statistics of Patients Receiving Win 8778

Patient	Age	Race*	Clinical Diagnosis†	Fundi‡ K-W	Renal§ Disease	Electro-cardiogram‖
1. S. J.	62	N	HCVD	III	0	IV
2. B. J.	55	W	HCVD	III	0	IV
3. H. N.	46	W	HCVD	III	++	III
4. J. R.	66	W	HCVD	II	+++	IV
5. S. N.	47	N	HCVD	II	++	IV
6. F. K.	59	W	HCVD	II	++	III
7. O. T.	58	W	HCVD	II	+	II
8. H. S.	60	N	HCVD	II	+	II
9. W. A.	54	N	HCVD	II	++	III
10. J. H.	48	N	HCVD	II	+++	IV

* Race: N = Negro; W = White.
† HCVD: Hypertensive cardiovascular disease.
‡ Keith-Wagener classification (graded 1–4).
§ Renal disease: + = normal or occasional albuminuria.
++ = albuminuria and elevated blood urea nitrogen.
+++ = albuminuria, elevated BUN and fixed specific gravity.
‖ Electrocardiograms: I = minimal *T* wave changes only.
II = hypertrophy of left ventricle without strain.
III = hypertrophy of left ventricle with strain.
IV = hypertrophy of left ventricle with strain and ischemia.

B. Win 12,512-2 (ganglionic blocking agent).

1. Laboratory Investigation. The drug was given to 26 dogs, in graded doses from 0.02 mg./kg. to 2 mg./kg. The pressor response to carotid occlusion, central vagal stimulation and norepinephrine administration was observed at the different doses employed. The depressor response to peripheral vagal stimulation was also observed as additional evidence of ganglionic blockade. The dogs were anesthetized with 30 mg./kg. of pentobarbital.

Observations on renal hemodynamics were made on three groups of dogs, employing 0.1, 0.5 and 1 mg./kg. The effect on blood pressure was observed concomitantly with the effect on glomerular filtration rate, renal plasma flow, hematocrit and changes in the excretion of water and electrolytes as well as the serum electrolyte pattern.

2. Clinical Investigation. The effect of the drug was then observed in 10 male patients with hypertensive cardiovascular disease. The vital statistics of these patients are presented in table 2. The drug was given orally

in exactly the same fashion on a given day at 10 a.m. in an incremental fashion until a significant hypotensive response was elicited, a method very similar to that used in the evaluation of Win 8778. After the optimal oral dose was found the drug was given intramuscularly in an incremental fashion to determine the degree of absorption of the drug by comparing the two dosages which achieved a hypotensive response. After each patient had exhibited a significant hypotensive effect due to the blocking agent, he was then given an infusion of norepinephrine to determine the reversibility of the hypotension. The patients were maintained on the hypertensive ward exactly as described in the investigation of Win 8778.

TABLE 2

Vital Statistics of Patients Receiving Win 12,512-2

Patient	Age	Race*	Clinical Diagnosis†	Fundi‡ K-W	Renal§ Disease	Electrocardiogram‖
1. H. S.	65	N	HCVD	II	+	II
2. W. A.	54	N	HCVD	II	++	III
3. R. C.	58	N	HCVD	III	+	IV
4. S. J.	62	N	HCVD	III	0	IV
5. B. J.	55	W	HCVD	III	0	IV
6. H. N.	46	W	HCVD	III	++	III
7. J. R.	66	W	HCVD	II	+++	IV
8. O. T.	58	W	HCVD	II	+	II
9. M. H.	62	W	HCVD	II	++	III
10. F. H.	55	N	HCVD	II	++	III

See table 1 for key to abbreviations.

C. Win 13,596-2 (central and ganglionic blocking agent).

1. Laboratory Investigation. The drug was given intravenously to two groups of dogs. The first group (eight dogs) received 0.5 mg./kg. of 13,596-2, and the second group (eight dogs) received 1.0 mg./kg. Observations were made on mean blood pressure, glomerular filtration rate, renal blood flow, hematocrit and urine flow at two intervals. The first observation consisted of two 10-minute periods immediately after the administration of the drug (D1), and the second observation consisted of two 10-minute periods one hour after the administration of the drug (D2). The dogs were anesthetized with 30 mg./kg. of pentobarbital.

2. Clinical Investigation. The effect of the drug was then observed in five male patients with hypertensive cardiovascular disease. The vital statistics of these patients are presented in table 3. The drug was given intramuscularly (only) in an incremental fashion on a given day at 10 a.m. in an effort to achieve a significant hypotensive effect. However, rather than a reduction in blood pressure, an increase in blood pressure was observed. The dose recorded is the highest one employed in the given patient: in the first two it was 0.3 mg./kg.; in the last three, it was 0.5 mg./kg.

TABLE 3

Vital Statistics of Patients Receiving Win 13,596-2

Patient	Age	Race*	Clinical Diagnosis†	Fundi‡ K-W	Renal§ Disease	Electro-cardiogram‖
1. M. D.	65	W	MHCVD	III	+++	IV
2. O. T.	58	W	HCVD	II	+	III
3. J. H.	48	W	HCVD	II	++++	IV
4. J. J.	60	N	HCVD	II	+	III
5. H. W.	63	N	HCVD	II	++	IV

See table 1 for key to abbreviations.

RESULTS

A. Win 8778.

1. Laboratory Observations. Our laboratory investigation of this drug revealed that 0.5 mg./kg. produced a consistent reversal of the hypertensive effect associated with the administration of 10 μg/kg. of norepinephrine or epinephrine given intravenously as a single injection (figure 1). The pressor response to 50 μg/kg. of norepinephrine was blocked with a dose of Win 8778 of 1 mg./kg. The pressor response to carotid occlusion and central vagal stimulation was partially blocked at a dose of 1 mg./kg., and maximally blocked at a dose of 2 mg./kg.

The drug produced a significant reduction in blood pressure in the dogs studied at doses of Win 8778 of 0.5 mg./kg., 1.0 mg./kg. and 2.0 mg./kg. (table 4). In the nine dogs receiving 2 mg./kg. there was a reduction in the mean blood pressure from 111 mm. Hg to 91 mm. Hg 20 minutes after drug administration ($P < 0.05$). Prolonged follow-up after administra-

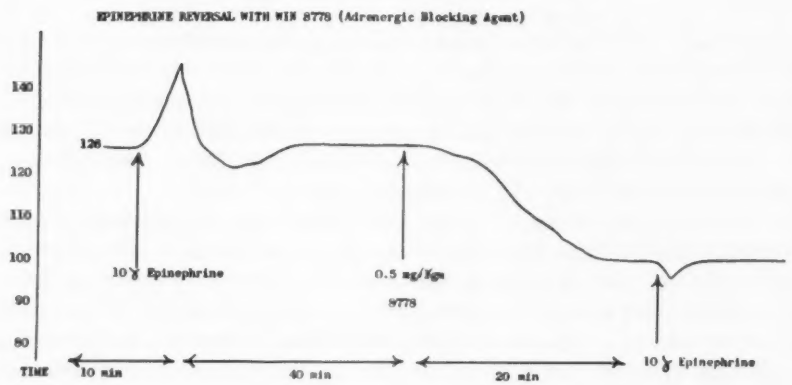


FIG. 1. Laboratory investigations of Win 8778 in dogs revealed reversal of norepinephrine-induced hypertension.

TABLE 4.—Renal Hemodynamic Response to Adrenergic Blockade with Win 8778

Dog No.	Mean Blood Pressure mm. Hg				Glomerular Filtration Rate c.c./min.				Renal Plasma Flow* c.c./min.				Renal Blood Flow c.c./min.				Hematocrit				Renal Vascular Resistance			
	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3
Group A Dose = 0.5 mg./kg.																								
1	124	110	101	135	68	76	67	67	232	301	255	161	363	485	392	252	36	38	35	36	.34	.23	.26	.54
2	150	129	111	110	51	61	54	62	183	252	223	192	261	371	319	287	30	32	30	33	.57	.35	.35	.38
3	132	117	123	146	49	56	51	59	163	213	182	139	267	355	303	232	39	40	40	40	.49	.33	.41	.63
4	116	102	95	134	75	64	66	71	245	245	208	165	408	438	359	284	40	44	42	42	.28	.23	.26	.47
Mean	131	115	108	131	61	64	60	65	206	253	217	164	325	412	343	264	36	39	37	38	.42	.29	.32	.51
% of control		88	82	100		105	98	107		123	105	80		127	106	81		108	103	106		69	76	121
Group B Dose = 1.0 mg./kg.																								
5	148	86	60	41	46	58	27	19	158	219	123	82	203	292	160	104	22	25	23	21	.73	.29	.38	.39
6	124	126	123	148	58	55	56	58	180	193	159	124	257	297	245	191	30	35	35	35	.48	.42	.50	.77
7	126	106	99	142	58	52	51	51	173	186	182	111	237	266	249	159	27	30	27	30	.53	.40	.40	.89
8	140	85	71	57	41	26	—	31	127	101	—	114	235	194	—	224	46	48	49	49	.60	.44	—	.25
9	150	159	152	141	56	52	54	65	120	167	140	179	185	257	215	271	35	35	35	34	.81	.62	.71	.52
Mean	138	112	101	106	52	49	47	45	152	173	151	122	223	261	217	190	32	35	34	34	.63	.43	.50	.56
% of control		81	73	77		94	90	87		114	99	80		117	97	85		109	106	106		68	79	89
Group C Dose = 2.0 mg./kg.																								
10	149	85	106	139	45	39	46	57	127	122	113	137	276	254	231	269	54	52	51	49	.54	.33	.46	.52
11	93	69	85	106	28	24	23	17	174	127	95	71	300	202	138	103	42	37	31	31	.31	.34	.62	1.03
12	93	82	45	89	41	46	34	34	125	159	126	85	187	237	180	129	33	33	30	34	.50	.35	.25	.69
13	87	72	75	83	44	47	44	49	125	141	118	124	171	199	159	163	27	29	26	24	.51	.36	.47	.51
14	128	117	131	141	44	40	39	40	119	114	97	88	216	219	198	180	45	48	51	51	.59	.53	.66	.78
15	108	102	106	117	28	31	37	34	75	108	134	101	109	159	203	155	31	32	34	35	.99	.64	.52	.75
16	109	91	74	90	35	32	25	28	101	133	102	106	160	211	152	158	37	37	33	33	.68	.43	.49	.57
17	108	100	101	121	63	67	61	63	209	278	224	185	332	456	361	294	37	39	38	37	.33	.22	.28	.41
18	122	105	81	120	61	65	51	46	168	211	180	119	263	346	273	175	36	39	34	32	.46	.30	.30	.69
Mean	111	91	89	112	43	43	40	41	136	155	132	113	224	254	211	181	38	38	36	36	.55	.39	.45	.66
% of control		82	80	101		100	93	95		114	97	83		113	94	81		100	95	95		71	82	120
P value† <		.05	.05	.50		.50	.40	.50		.20	.50	.20		.20	.50	.20		.50	.30	.30		.001	.30	.50

* Renal plasma flow = clearance of para-aminohippurate.

† $t = \bar{x}\sqrt{\frac{n(n-1)}{sx^2}}$; statistical analysis by R. A. Seibert.

Key to abbreviations:

C = Control.

D_1 = Average of two successive periods after drug administration intravenously.

D_2 = Average of two successive periods 50 minutes after drug administration intravenously.

D_3 = Average of two successive periods 120 minutes after drug administration intravenously.

TABLE 5.—Effect of Adrenergic Blockade with Win 8778 on Water and Electrolyte Excretion

Dog No.	Urine Volume c.c./min.				Plasma Sodium mEq./L.			Plasma Potsasium mEq./L.			Urine Sodium μEq./min.				Urine Potassium μEq./min.				Wt. in Kg.	Dose mg./kg.
	C	D_1	D_2	D_3	C	D_1	D_3	C	D_1	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3		
Group A Dose = 0.5 mg./kg.																				
1	3.3	3.5	2.3	2.2	151	151	150	2.7	2.9	3.1	206	432	234	13	41	64	57	53	18.0	.5
2	1.1	2.6	2.6	2.2	142	143	143	3.0	2.4	2.0	22	275	306	121	13	31	29	34	18.0	.5
3	1.4	4.4	2.7	2.8	143	144	151	2.8	2.3	2.3	53	280	124	160	22	50	39	50	13.0	.5
4	1.2	1.4	1.4	5.5	132	134	136	2.9	3.1	3.4	136	163	47	78	100	51	48	78	18.0	.5
Mean	1.8	3.0	2.3	3.2	142	143	145	2.9	2.7	2.7	104	288	178	93	44	49	43	54	16.8	.5
% of control		167	128	178		101	102		93	93		277	171	89		111	98	123		
Group B Dose = 1.0 mg./kg.																				
5	1.1	1.8	0.7	0.6	—	—	—	—	—	—	22	43	13	15	27	32	38	86	18.0	1.0
6	2.6	2.9	3.5	2.6	135	136	139	2.3	2.8	2.9	256	299	254	181	41	48	63	57	16.0	1.0
7	3.3	1.6	3.2	4.0	141	144	141	2.6	1.8	2.8	306	186	208	207	40	37	44	57	16.0	1.0
8	0.8	0.6	0.4	0.7	137	140	142	2.7	2.3	1.8	45	32	—	12	26	18	—	15	10.0	1.0
9	1.1	1.4	3.2	2.8	134	134	138	3.1	3.3	2.9	61	47	92	383	42	62	88	121	11.0	1.0
Mean	1.8	1.7	2.2	2.1	137	139	140	2.7	2.6	2.6	138	121	142	160	35	39	58	67	14.2	1.0
% of control		94	122	117		101	102		96	96		88	103	116		111	166	191		
Group C Dose = 2.0 mg./kg.																				
10	1.1	0.8	1.2	3.6	151	151	149	2.3	3.0	2.1	88	86	47	215	13	15	21	32	12.0	2.0
11	0.6	0.7	0.5	0.5	145	152	143	3.6	2.2	2.9	16	15	13	12	8	7	8	9	10.0	2.0
12	0.5	1.0	0.4	0.3	147	147	147	2.7	3.2	2.1	16	100	12	10	10	38	6	12	10.0	2.0
13	2.0	3.2	2.6	2.1	142	142	147	3.6	3.0	3.2	320	310	100	178	38	46	33	52	9.5	2.0
14	1.0	1.6	2.5	3.3	141	141	154	3.6	3.1	4.8	61	104	91	132	10	15	24	28	11.0	2.0
15	0.5	1.0	4.2	3.6	137	135	141	3.9	3.5	3.9	25	52	119	90	10	19	63	78	12.0	2.0
16	1.4	1.8	1.1	1.7	139	136	141	3.0	2.6	2.8	30	112	34	65	18	29	27	29	10.0	2.0
17	0.6	1.3	1.6	2.5	140	139	141	3.7	3.4	3.9	145	297	226	248	16	32	37	54	12.0	2.0
18	1.2	2.7	1.7	3.8	136	135	147	2.9	2.4	2.8	141	325	62	64	36	51	38	37	16.0	2.0
Mean	1.0	1.6	1.8	2.4	142	142	146	3.3	2.9	3.2	94	156	78	113	18	28	29	37	11.4	2.0
% of control		160	180	240		100	103		88	97		166	83	120		156	161	206		
P value† < (Group C only)		.01	.10	.01		.50	.10		.20	.50		.05	.50	.50		.01	.10	.05		

Key to Table 5: $t = \bar{x}\sqrt{\frac{n(n-1)}{sx^2}}$.

C, D_1, D_2, D_3 = See table 4 for key to abbreviations.

tion of the drug did not show any additional significant reduction in blood pressure, and by two hours the blood pressure had returned to control levels.

There was no significant decline in glomerular filtration rate associated with the reduction in blood pressure. There was a slight initial increase ($P < 0.20$), followed by a reduction in renal blood flow from 224 c.c. per minute after drug administration to 181 c.c. per minute two hours later. This latter effect was not statistically significant ($P < 0.20$), and was observed at a time when the blood pressure had already returned to control levels, illustrating that the acute reduction in blood pressure is not associated with a significant decline in renal blood flow. There was no significant change in hematocrit or plasma sodium and potassium concentrations. Increases in urine volume and in sodium and potassium excretion were not great, but they were consistent enough to be statistically significant ($P < 0.05$) immediately after drug administration (table 5).

2. Clinical Observations. When the drug was given to 10 hypertensive male patients, there was a reduction in the upright mean blood pressure from 137 mm. Hg to 90 mm. Hg ($P < 0.001$), a highly significant fall (table 6). The onset of this blood pressure reduction occurred at an average of 69 minutes following the administration of the drug by mouth. The effect of this reduction lasted for an average of 19 hours. There was also a partial effect for a total of 25 hours. The average dose resulting in this decline in blood pressure was 104 mg. of Win 8778. The most frequent side effects were angina and agitation. These symptoms were observed in seven of the 10 patients studied. One man exhibited an occurrence of paroxysmal auricular fibrillation during administration of the drug. No episodes of syncope, constipation, diarrhea or nausea and vomiting were observed. When the patients exhibited the most marked hypotensive effect they were given an intravenous infusion of norepinephrine, which was associated with absolutely no increase in blood pressure, illustrating effective adrenergic blockade (figure 3).

Win 8778 was also administered intravenously to seven hypertensive patients. None of the seven patients obtained a reduction in blood pressure. The parenteral form of this drug was retested by the pharmaceutical chemist and found to be unstable and pharmacologically impotent.* Therefore, we have no method for determining the effectiveness after parenteral administration to man, or the exact gastrointestinal absorption of this drug, but the fact that the parenteral hypotensive dose in the dogs was 0.5 to 1.0 mg./kg. bears a striking similarity to the hypotensive oral dose in humans, which was approximately 1.0 mg./kg. This suggests a high degree of intestinal absorption of the drug. This is in keeping with the fact that humans are at least as sensitive (if not more so) to adrenergic blocking agents as are laboratory animals.[3]

* This occurred only in the preparation of the sterile (autoclaved) ampules for clinical use, and was not observed in the material used in the laboratory, which was prepared for each experiment.

TABLE 6

The Response in Blood Pressure to the Administration of Single Doses of Win 8778 Given Orally

Patient	Control Blood Pressure				Maximal Blood Pressure				Upright Mean B. P.*		B. P. Reduction			Dose (mg.)	Side Effects
	Recumbent		Upright		Recumbent		Upright								
	S	D	S	D	S	D	S	D	Control	Drug	Onset (min.)	Duration Total	Part. (hrs)		
1. S. J.	160	110	146	96	140	90	102	62	113	75	15	16	24	100	Angina
2. B. J.	200	120	160	120	154	100	80	60	133	67	60	24	36	80	Nervous
3. H. N.	260	170	230	160	210	130	140	110	183	120	60	16	24	80	Angina Nervous
4. J. R.	200	124	180	114	180	110	90	60	136	70	30	24	30	100	Auricular fibrillation
5. S. L.	170	120	170	120	170	100	100	80	137	87	60	16	20	200	0
6. F. K.	200	120	160	110	160	100	110	80	127	90	45	20	24	80	0
7. O. T.†	175	105	170	105	160	90	110	70	126	83	120	20	24	100	Angina
8. H. S.†	160	110	140	110	160	90	130	80	120	97	120	18	24	100	Nervous
9. W. A.	190	110	185	115	170	100	110	70	138	83	120	18	24	100	Angina
10. J. H.†	230	150	200	140	200	130	160	110	160	127	60	16	24	100	0
Average	195	124	174	119	170	104	113	78	137	90	69	19	25	104	—

S = Systolic; D = Diastolic.

* = Mean blood pressure, diastolic plus ⅓ pulse pressure.

† = Patient also received Win 8778 intravenously without change in blood pressure.

B. Win 12,512-2.

1. Laboratory Observations. This drug was found to be an effective ganglionic blocking agent (figure 2). A dose of 0.02 mg./kg. produced partial and inconstant blockade of the pressor response to carotid occlusion, whereas a dose of 0.05 mg./kg. produced consistent blockade of this reflex.

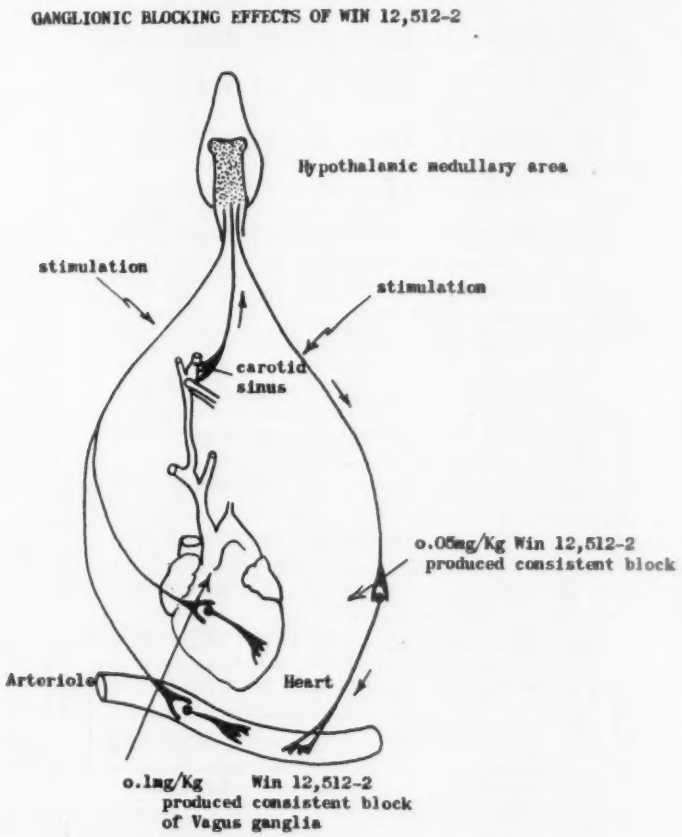


FIG. 2. Laboratory investigations of Win 12,512-2 indicate blockade of parasympathetic and sympathetic ganglia.

A dose of 0.1 mg./kg. produced complete blockade of the hypotensive response to peripheral vagal stimulation. There was no blockade of the vasopressor response to intravenous norepinephrine. These observations indicate ganglionic blockade, although an additional central effect of the drug has not been ruled out by these observations.

TABLE 7

Renal Hemodynamic Response to Win-12,512-2

Dog Number	Wt. kg.	Dose mg./kg.	Mean Blood Pressure mm. Hg				Glomerular Filtration Rate c.c./min.				Renal Plasma Flow c.c./min.				Renal Blood Flow c.c./min.				Hematocrit			
			C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_2	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3
Sub-group A																						
1	19.0	.1	145	117	94	106	60	56	38	38	109	144	160	146	173	232	239	209	37	38	33	30
2	20.0	.1	102	76	77	90	51	34	52	54	184	111	183	189	317	209	345	350	42	47	47	46
3	21.0	.1	152	151	140	153	72	69	66	65	195	224	179	151	361	407	331	256	46	45	46	41
4	14.0	.1	134	126	128	140	66	69	61	63	177	219	194	134	260	348	313	203	32	37	38	34
Mean	18.5	.1	133	118	110	122	62	57	54	55	166	175	179	155	278	299	307	255	39	42	41	38
% of control				89	83	92		92	87	89		105	108	93		108	110	92		108	105	97
Sub-group B																						
5	20.0	.5	135	102	89	113	67	70	70	61	166	212	230	148	286	359	383	228	42	41	40	35
6	17.0	.5	101	95	87	110	45	45	31	32	141	142	126	90	188	189	168	118	25	25	25	24
7	16.0	.5	132	118	107	125	51	57	51	50	130	166	149	116	210	263	229	178	38	37	35	35
8	20.0	.5	119	84	104	117	71	80	82	63	196	237	270	168	288	334	386	230	32	29	30	27
9	16.0	.5	123	122	114	137	53	57	54	47	159	178	150	110	237	270	231	164	33	34	35	33
Mean	17.8	.5	122	104	100	120	57	62	58	51	158	187	185	126	242	283	279	184	34	33	33	31
% of control				85	82	98		109	102	89		118	117	80		117	115	76		97	97	91
Sub-group C																						
10	12.0	1.0	97	82	69	86	35	37	39	34	84	109	107	84	124	158	145	117	32	31	26	28
11	14.0	1.0	134	97	79	84	43	47	46	37	140	215	164	138	215	331	260	271	35	35	37	49
12	18.0	1.0	117	46	38	42	98	11	1	1	340	108	1	1	500	174	——	——	32	38	38	38
13	17.0	1.0	144	92	68	61	47	63	49	40	182	223	238	206	294	372	335	294	38	40	29	30
14	10.0	1.0	145	84	67	84	34	31	28	28	90	103	77	62	170	184	118	98	47	44	35	37
15	16.0	1.0	112	91	101	123	37	40	38	31	92	116	86	63	161	204	146	115	43	43	41	45
16	10.0	1.0	80	61	60	95	49	50	44	31	122	155	129	92	163	199	163	116	25	22	21	21
17	11.0	1.0	96	52	62	82	42	32	27	24	143	138	98	66	251	234	151	108	43	41	35	39
Mean	13.5	1.0	116	76	68	82	48	39	34	28	149	146	113	89	235	232	188	160	37	37	33	36
% of control				66	59	71		81	71	58		98	76	60		99	80	68		100	89	97
P value‡ <				.001	.01	.05		.50	.30	.20		.50	.50	.20		.50	.50	.20		.50	.20	.50

Key: C = Control observations—average of 3–10 minute periods.
D_1 = Observations immediately after administration of drug (12,512-2)—average of 3–10 minute periods.
D_2 = Observations 1 hour after administration of drug—average of 2–10 minute periods.
D_3 = Observations 2 hours after administration of drug—average of 2–10 minute periods.

‡ = Dogs number 10 to 17; $t = \bar{x}\sqrt{\frac{n(n-1)}{sx^2}}$.

TABLE 8

Effect of 12,512-2 on Water and Electrolyte Excretion

Dog Number	Wt. kg.	Dose mg./kg.	Urine Volume c.c./min.				Plasma Sodium mEq./L.				Plasma Potassium mEq./L.				Urine Sodium μEq./min.				Urine Potassium μEq./min.			
			C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_2	D_3	C	D_1	D_3	D_2
Sub-group A																						
1	19.0	.1	2.1	1.8	1.0	1.4	127	127	130	132	2.2	2.0	1.6	1.7	24	23	10	7	31	27	17	24
2	20.0	.1	0.3	0.2	0.6	1.5	134	139	135	136	2.6	2.1	2.1	2.9	22	10	9	24	39	12	34	37
3	21.0	.1	0.3	1.6	0.9	1.9	137	137	139	144	2.2	1.9	2.4	2.7	90	86	48	82	62	38	39	54
4	14.0	.1	0.9	3.1	2.7	2.3	148	151	149	154	2.1	2.0	2.2	2.6	66	338	269	153	37	57	63	63
Mean	18.5	.1	0.9	1.7	1.3	1.8	137	139	138	142	2.3	2.0	2.1	2.5	51	114	84	67	42	34	38	45
% of control				189	144	200		101	101	104		87	91	109		224	165	131		81	90	107
Sub-group B																						
5	20.0	.5	1.1	3.4	2.6	5.0	138	143	143	154	2.6	2.4	2.4	2.6	90	469	257	126	32	63	55	16
6	17.0	.5	2.6	4.2	2.0	1.8	155	158	157	161	2.3	2.0	2.2	2.4	63	228	153	70	56	52	27	29
7	16.0	.5	1.5	2.8	1.7	3.5	144	148	149	142	2.5	2.3	2.5	2.7	198	375	158	217	36	32	32	57
8	20.0	.5	1.3	1.2	7.7	6.8	147	150	157	152	2.5	2.2	1.9	2.4	168	73	124	110	31	44	83	55
9	16.0	.5	1.9	4.1	3.3	3.8	139	136	137	140	2.5	2.8	2.3	2.7	198	441	240	200	38	41	39	53
Mean	17.8	.5	1.7	3.1	3.5	4.2	145	147	149	150	2.5	2.3	2.3	2.6	143	317	187	145	39	46	47	42
% of control				182	206	247		101	103	103		92	92	104		222	131	101		118	121	108
Sub-group C																						
10	12.0	1.0	0.7	1.0	0.8	1.1	137	137	140	144	3.8	3.0	2.5	2.8	6	70	37	69	16	35	23	22
11	14.0	1.0	0.6	2.5	1.5	2.3	135	135	140	141	3.7	2.9	3.2	3.1	41	349	117	120	31	46	49	51
12	18.0	1.0	0.9	0.3	0.2	0.2	136	139	143	147	4.0	3.3	3.4	4.4	35	12	2	4	37	4	1	1
13	17.0	1.0	0.6	1.6	1.2	0.9	137	137	142	140	3.2	2.6	2.2	2.6	31	202	86	40	5	32	20	19
14	10.0	1.0	1.1	1.4	0.8	1.8	139	144	141	150	3.3	2.8	3.2	2.8	32	149	59	142	22	31	27	29
15	16.0	1.0	0.8	2.3	2.1	2.4	144	138	139	149	3.8	3.6	3.3	3.4	17	156	99	107	20	59	45	50
16	10.0	1.0	0.5	1.1	1.0	0.8	137	137	137	139	3.3	2.6	2.6	3.1	22	114	35	18	12	29	23	21
17	11.0	1.0	1.4	0.7	0.7	0.8	—	—	—	—	2.3	1.4	2.7	3.3	76	35	11	27	32	19	18	17
Mean	13.5	1.0	0.8	1.4	1.0	1.3	138	138	140	144	3.4	2.8	2.9	3.2	33	136	56	66	22	32	26	26
% of control				175	125	163		100	101	104		82	85	94		412	170	200		145	118	118
P Value‡ <				.20	.50	.20		.50	.30	.10		.001	.05	.50		.05	.30	.20		.30	.50	.50

Key to abbreviations—See Table 7 for C, D_1, D_2 and D_3.

Renal hemodynamic response to Win 12,512-2 was observed in three groups of dogs at a dose of 0.1 mg./kg. and 0.5 mg./kg. and 1 mg./kg. (table 7). A maximal hypotensive response was observed at a dose of 1 mg./kg. In the group of dogs (Subgroup B) which received 0.5 mg./kg., the blood pressure declined to 82% of control at the end of one hour, and to 59% ($P < 0.01$) of control after one hour in the group of dogs (Subgroup C) which received 1 mg./kg. After two hours the blood pressure had returned to control values in the dogs receiving 0.5 mg./kg., but in those receiving 1 mg./kg. (Subgroup C, table 7), it remained depressed in most of the animals ($P < 0.05$). These changes were associated with decline in glomerular filtration rate to 89% of control at the end of two hours in Subgroup B (0.5 mg./kg.), and to 58% of control in Subgroup C (1 mg./kg.), which was not statistically significant ($P < 0.20$). The renal plasma flow decreased only slightly in the dogs in Subgroup B, but decreased to 60% of control in those in Subgroup C. There was no significant change in the hematocrit.

The urine volume tended to be increased in all groups of dogs, that is, to 175% of control during the first 30 minutes. It then decreased to 125% of control after one hour, and increased again to 163% of control after two hours. These observations were not consistent enough to be statistically significant. There was no significant change in plasma sodium, but there was a temporary decrease in plasma potassium concentration ($P < 0.001$), probably due to the infusion of fluids. Urinary sodium excretion (table 8) increased temporarily ($P < 0.05$), but rapidly returned toward the control values.

2. Clinical Observations. Since the drug was found to be safe in the dog, it was tested in 10 hypertensive patients on the hypertensive ward. The drug was given in an incremental fashion as described under Materials and Methods, with the following results (table 9): When the drug was given intramuscularly there was an average decline in the upright blood pressure from 130 to 89 mm. Hg; and when given by mouth, the decline was from 128 to 85 mm. Hg. The average onset of this blood pressure effect was 86 minutes after administration when given intramuscularly and 150 minutes when given orally. The duration of effect was 13 hours when given intramuscularly and 18 hours when given orally, but there was also an additional partial reduction in blood pressure for 19 hours after the intramuscular route and 28 hours after the drug had been given orally. The average dose was 5 mg. intramuscularly and 460 mg. orally, indicating that the drug is roughly 1% absorbed when taken by mouth. The side effects associated with these single doses were insignificant. At the height of the blood pressure reduction in each of these cases, an infusion of norepinephrine was given intravenously, which resulted in a prompt return of the blood pressure to the control state. This is illustrated in figure 3.

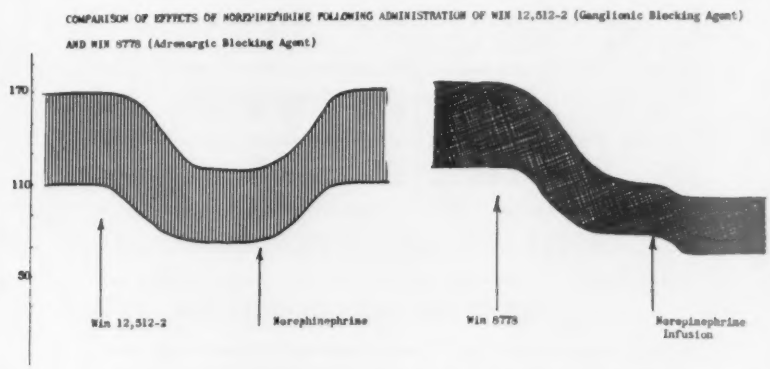


FIG. 3. Comparison of effects of norepinephrine after Win 8778 and Win 12,512-2.

C. Win 13,596-2.

1. Laboratory Observations. At both doses there was a reduction in mean blood pressure (table 10). After a dose of 0.5 mg./kg. there was a decline from 112 to 93 mm. Hg within 20 minutes (83% of control), and to 91 mm. Hg after one hour (81% of control). These changes were highly significant ($P < .01$). During the first 20 minutes of this reduction of mean blood pressure there was no significant change in glomerular filtration rate or renal blood flow. After prolonged reduction (one hour) of blood pressure, there was a slightly greater decline in glomerular filtration rate (to 85% of control) and in renal blood flow (to 85% of control), but these changes were not statistically significant. There was no significant change in hematocrit or urine flow. After a dose of 1.0 mg./kg. of 13,596-2, similar changes were observed, but the degree of change was no greater.

2. Clinical Observations. Since the drug was found to be both safe and effective in the laboratory animal, it was tested in five male patients who had hypertension. Without exception there was an increase in mean blood pressure, with the average increase being from 136 mm. Hg in the control state to 163 mm. Hg after the drug (table 11). This increase occurred within 126 minutes as an average and lasted 19 hours. The average dose producing this change was 30 mg. of 13,596-2. No side effects were noted.

DISCUSSION

Although the fundamental etiologic factors involved in the production of hypertension have not been clarified, the availability of drugs of three main groups has permitted us to develop rational therapeutic approaches to this disease. In previous publications we have reported our evaluation of hypotensive agents with predominant central action (rauwolfia preparations, hydralazine, and veratrum compounds), ganglionic blocking agents

TABLE 9

The Response in Blood Pressure to the Administration of Single Doses of Win 12,512-2

Patient	Control Blood Pressure				Maximal B. P. Response				Upright Mean B. P.*		B. P. Reduction			Dose (mg.)	Side Effects
	Recumbent		Upright		Recumbent		Upright								
	S	D	S	D	S	D	S	D	Control	Drug	Onset (min.)	Duration Total	Part. (hrs.)		
1. H. S.—I. M.	180	110	160	110	144	88	96	70	127	79	60	12	18	4	++
P. O.	172	100	150	100	124	84	90	70	117	77	180	16	24	400	+
2. W. A.—I. M.	180	100	160	110	160	100	130	90	127	103	60	10	18	6	0
P. O.	190	100	170	102	160	90	90	68	125	75	60	20	36	600	++
3. R. C.—I. M.	184	104	170	120	130	98	76	54	137	61	30	16	18	8	+
P. O.	194	114	174	110	160	114	110	82	131	91	150	14	24	400	0
4. S. J.—I. M.	170	100	150	110	120	90	100	70	123	80	15	12	18	6	0
P. O.	160	120	150	100	110	90	80	60	117	67	150	12	18	400	0
5. B. J.—I. M.	160	98	130	90	160	100	120	60	103	80	180	12	18	6	+
P. O.	180	102	160	100	160	100	118	60	120	79	240	12	18	400	+
6. H. N.—I. M.	170	110	160	100	150	90	110	70	120	83	60	8	16	2	0
P. O.	184	114	150	110	180	110	140	80	123	100	180	16	24	600	0
7. J. R.—I. M.	210	110	178	100	180	180	150	80	126	103	180	10	16	4	0
P. O.	218	114	190	104	150	90	100	80	133	87	120	24	36	400	0
8. O. T.—I. M.	190	120	180	110	170	100	130	80	133	97	120	16	24	4	0
P. O.	190	100	140	90	170	100	120	70	107	87	180	18	24	400	0
9. M. H.—I. M.	200	110	190	110	190	100	140	80	137	100	60	16	24	4	0
P. O.	200	110	190	110	190	90	130	70	137	86	120	24	36	400	0
10. F. H.—I. M.	220	140	210	145	200	130	150	80	167	103	90	18	24	6	0
P. O.	220	140	210	145	190	120	130	80	167	97	120	24	36	600	0
Average I. M.	186	110	169	111	160	107	120	73	130	89	86	13	19	5	—
P. O.	191	111	168	107	159	99	111	73	128	85	150	18	28	460	—

I. M. = Intramuscularly; P. O. = Orally.
S = Systolic. D = Diastolic.

* = Upright mean blood pressure—mean blood pressure, diastolic plus $\frac{1}{3}$ pulse pressure.

TABLE 10.—Renal Hemodynamic Response to Win 13,596-2

Dog No.	Mean Blood Pressure mm. Hg			Glomerular Filtration Rate c.c./min.			Renal Blood Flow c.c./min.			Hematocrit			Urine Volume c.c./min.			Weight in Kg.
	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	
Group A Dogs received 0.5 mg./kg. of Win 13,596-2																
1	124	78	66	54	42	30	249	222	136	45	45	42	1.1	0.4	0.4	13.0
2	130	108	78	29	33	27	132	174	155	47	50	47	0.8	0.8	0.8	9.0
3	100	83	105	54	49	49	304	229	161	21	20	21	1.4	1.2	0.8	14.0
4	147	140	110	73	74	61	444	548	503	41	44	42	1.6	4.7	2.5	23.5
5	94	89	81	46	52	38	287	360	209	39	42	36	1.0	1.8	2.5	12.5
6	127	95	97	35	37	48	208	271	255	36	37	38	0.4	1.8	2.6	12.0
7	88	75	122	54	55	45	204	240	134	20	20	23	0.5	1.2	0.9	16.0
8	89	76	71	75	68	58	284	287	237	38	38	41	0.9	3.0	1.7	18.0
Mean	112	93	91	53	51	45	264	291	224	36	37	36	1.0	1.9	1.5	14.8
% of control		83	81		96	85		110	85		103	100		190	150	
P value*		.01	.01		.50	.10		.30	.20		.20	.50		.10	.20	
Group B Dogs received 1 mg./kg. of Win 13,596-2																
1	109	96	79	38	38	35	175	189	183	41	39	37	0.3	2.1	2.0	12.0
2	90	63	78	89	69	74	415	467	493	40	42	45	0.5	0.4	3.0	17.0
3	99	93	81	76	69	54	385	419	226	38	41	32	1.9	1.5	1.2	15.0
4	109	101	81	44	46	53	231	278	329	38	40	32	0.5	0.5	1.6	20.0
5	98	94	99	46	54	48	277	296	208	40	25	25	0.5	0.8	1.1	13.0
5	109	70	62	51	42	25	239	234	103	36	35	33	0.9	0.9	0.6	13.0
7	102	87	79	43	47	38	168	269	203	35	35	35	0.6	2.0	2.4	9.0
8	137	120	82	53	49	41	249	254	241	29	29	29	0.6	1.4	1.4	13.0
Mean	107	91	80	55	52	46	267	301	248	37	36	34	0.7	1.2	1.7	14.0
% of control		85	75		95	84		113	93		97	92		171	243	
P value*		.01	.01		.40	.10		.20	.50		.50	.10		.20	.10	

* = $t = \bar{x}\sqrt{\frac{n(n-1)}{sx^2}}$ · statistical analysis by R. A. Seibert.

C = Control.
D_1 = Two 10 minute periods after drug.
D_2 = Two 10 minute periods one hour after drug.

TABLE 11

The Response in Blood Pressure to the Administration of Single Doses of Win 13,596-2 Intramuscularly

Patient	Control Blood Pressure				Maximal Blood Pressure Response				Upright Mean Blood Pressure		Blood Pressure Increase		Dose Mg.	Side Effects
	Supine		Upright		Supine		Upright		Control	Drug	Onset	Duration		
	S	D	S	D	S	D	S	D						
1. M. D.	210	135	250	150	270	140	290	160	183	203	90	12	20	None
2. D. T.	200	110	190	110	220	120	200	120	137	147	90	16	20	None
3. J. H.	240	140	210	130	240	150	220	140	157	167	120	18	36	None
4. J. J.	150	100	130	90	240	145	220	140	103	167	240	36	36	None
5. H. W.	160	80	140	80	210	126	190	100	100	130	90	12	36	None
Average	192	113	184	112	236	136	224	132	136	163	126	19	30	

(hexamethonium, pentolinium, and mecamylamine), and adrenergic blocking agents (Dibenzyline). Because of the continued increase in drugs being synthesized and presented for further investigation that fall into these three groups, it has become necessary that the technics used for the evaluation of these drugs be systematized and explicitly defined. These technics also permit us to establish certain criteria for the acceptance and further development of agents which are to be used for treating hypertension.

Depending upon the severity of the hypertensive state, various drugs may be used with beneficial clinical responses. We believe that in any particular group of hypotensive agents, an effective drug should fulfill at least three criteria: 1) it must be potent as an antihypertensive agent; 2) it must be uniform and predictable in its results; and 3) it should have a low toxicity.

The drugs under investigation in this study are illustrations of three broad groups of drugs, that is, potentially centrally acting agents, ganglionic blocking agents and adrenergic blocking agents. Win 8778, 9-(2-chloroethyl) ethylamino-methyl anthracine hydrochloride, a new beta-haloalkylamine derivative, has been studied as an adrenergic blocking agent. The initial pharmacologic observation showed it was several times more potent than Dibenzyline and distinctly less toxic.[4] Its structural formula is illustrated in figure 4. Furthermore, Win 8778 was found to have a rapid onset of adrenolytic action, with a long duration of effect.

Win 12,512-2, 3-(2-diethylamino-ethylamino)-8-(20 chlorobenzyl) nortropane bismethylbromide was reported by the original investigators [5] to be a ganglionic blocking agent whose potency exceeded that of hexamethonium by 15 times and whose duration of action exceeded that of hexamethonium by at least six times. The blood pressure fall occurred gradually, the maximal reduction occurring in 40 to 60 minutes, with recovery after about 200 minutes following a single intravenous injection. The cross-circulation experiments showed that Win 12,512-2 had a central hypotensive action.

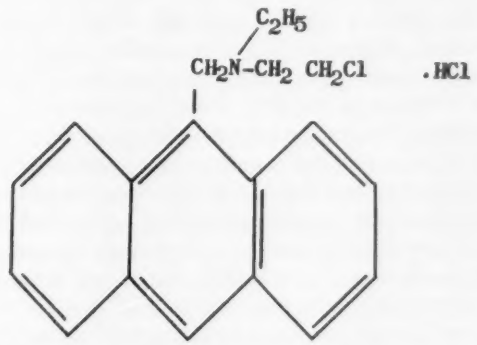


FIG. 4. Structural formula of Win 8778.

No obvious cardiac toxicity was observed. The ratio of ganglionic blockade in the dog (carotid occlusion response) to neuromuscular blockade was approximately the same for Win 12,512-2 and hexamethonium. Oral administration of Win 12,512-2 in the unanesthetized dog appeared to be about four times as effective as that observed with hexamethonium. The drug was well tolerated by rhesus monkeys when given three times daily for five consecutive days in doses of 1 and 5 mg./kg. orally. No hematologic changes were observed.[5]

Win 13,596-2, 3-(2-diethylaminoethyl) methylamino-8-(2-chlorobenzyl) nortropane bis-methochloride, was found to have sympathetic blocking activity as measured by inhibition of the pressor response to bilateral carotid occlusion. The peripheral ganglionic blocking activity of Win 13,596-2,

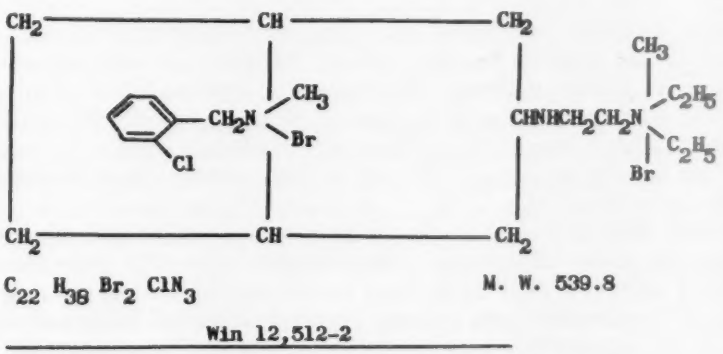
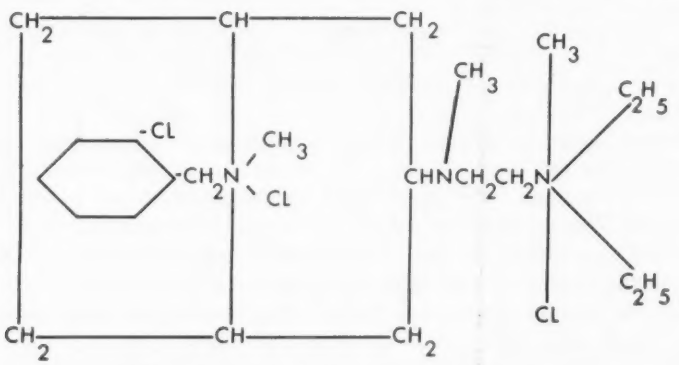


FIG. 5. Structural formula of Win 12,512-2.

as measured at the superior cervical ganglion in the dog and cat, ranged from 0.7 to three times as great as that of hexamethonium. Parasympathetic inhibitory activity indicated an activity much less than that observed by the carotid occlusion response in the dog, indicating selectivity of sympathetic suppression by comparison to the parasympathetic. The order of activity of Win 13,596-2 as judged by the vasodepressor response to peripheral vagal stimulation in the anesthetized dog and by the effect on heart rate following intravenous injection in the unanesthetized dog was found to be similar to that observed with hexamethonium. Cross-circulation studies indicate that both a peripheral mechanism and a central mechanism were involved in the production of a hypotensive response to Win 13,596-2 and hexamethonium in the dogs. A peripheral ganglionic blocking mechanism appeared to predominate in the case of hexamethonium, whereas the hypotensive response



STRUCTURAL FORMULA OF Win 13,596-2
[3-[(2-Diethylaminoethyl)methylamino]-8
-(2-chlorobenzyl)-nortropane bis-methochloride]

FIG. 6. Structural formula of Win 13,596-2.

to Win 13,596-2 appeared to be predominantly central in origin. Win 13,596-2 was found to be approximately 200 times as active as hexamethonium in producing a reversible hypotensive response following injection into the arterial circulation of the head of the recipient dog. Win 13,596-2 produced a fall in blood pressure following oral administration in the monkey, and was found to be very well tolerated in rhesus monkeys when administered orally twice daily.[6]

With these data in hand, the drugs were then subjected to similar investigation in our laboratories. The first drug, Win 8778 (an adrenergic blocking agent), fulfilled the first and second criteria—that is, the drug was a potent hypotensive agent and was apparently absorbed fairly well orally, but its clinical toxicity was too high and was similar to that seen with other adrenergic blocking agents. Thus the clinical symptoms of angina, palpita-

tion, tachycardia and nervousness were felt to be prohibitive of further clinical testing of the drug for the treatment of hypertensive vascular disease. Since lower doses are required in the treatment of peripheral vascular disease, it may have use there.

Win 12,512-2 (a ganglionic blocking agent) exhibited fulfillment of criteria 1 and 3—that is, it was a potent hypotensive agent and was associated with minimal toxicity, but its absorption was rather poor, only 1% being absorbed from the gastrointestinal tract. It is thus felt that this drug does not present any advantages over the presently available ganglionic blocking agents. Therefore, it has not been subjected to more widespread evaluation through the general hypertensive clinic out-patients.

Win 13,596-2 presented unusual features of differing action in the laboratory animal and human hypertensives. In the laboratory dog there was a prompt and significant reduction of mean blood pressure. In the hypertensive patient there was a consistent increase in blood pressure not influenced by position when the drug was given parenterally. Since the drug failed to fulfill the first criterion, that is, hypotensive potency, it was not subjected to further investigation, parenterally or orally. These observations suggest the necessity of screening unknown pharmacologic agents in both the laboratory animal as well as in the human patient who is to be treated. Since the drug has identical reactions in rats and humans but opposite reactions in humans and dogs, a reëvaluation of the choices of laboratory animals may be in order.

Thus it is hoped that, by the presentation of the general technic for the evaluation of the newer antihypertensive agents, various new drugs can be evaluated promptly and will become available to the clinician for addition to his armamentarium for the treatment of hypertensive vascular disease.

Conclusions

1. The technics for the evaluation of drugs to be used for the treatment of hypertension consist of the initial investigation, using laboratory animals for observing blood pressure response and the associated changes in renal hemodynamics and the excretion of water and electrolytes. Concurrent observations are made on the central effects and on the adrenergic and ganglionic blocking properties of the drug being tested. The drug is then studied in a limited number of hypertensive patients under controlled hypertensive ward conditions in which the drug is evaluated from the standpoint of an accurate measurement of dosage by mouth as well as parenterally, and the determination of the time of onset and duration of its effect. Observations are made of clinical toxicity in terms of renal, electrocardiographic and other effects.

2. The results of the present study indicate that Win 8778 is a potent adrenergic blocking agent, which is well absorbed orally but is associated with enough side effects to preclude its employment clinically for the treat-

ment of hypertensive cardiovascular disease. Win 12,512-2, a ganglionic blocking agent, is a potent hypotensive agent with a low toxicity, but is poorly absorbed and therefore does not fulfill the criteria for clinical treatment of hypertensive cardiovascular disease. Win 13,596-2, an agent with central as well as ganglionic blocking properties, is a potent hypotensive agent in the laboratory dog but has distinct hypertensive effects in human hypertensive patients. Further studies on this drug were not performed.

Summario in Interlingua

Ben que le factores etiologic fundamental que es implicate in le production de hypertension es non ancora clarificate, le disponibilitate de tres major gruppos de drogas has permittite a nos disveloppar procedimentos rational in le tractamento de iste morbo. A causa del crescente numero de drogas que se presenta al investigation, il deveni de plus in plus urgente que nos establi non solmente specific criterios que le nove agentes debe satisfacer sed etiam que nos defini explicitemente le technicas que es usate in lor evalutation.

In le evalutation de omne nove droga antihypertensive, le investigation initial require le uso de animales laboratorial. In iste animales on observa non solmente le responsa del pression sanguinee sed etiam le associate alterationes del hemodynamica renal e le excretion de aqua e electrolytos. Observationes simultanee es facite in re le effectos central e le proprietates de blocage adrenergic e ganglionic del drogas testate. Postea le droga es studiate in un numero limitate de patientes hypertensive. Hic illo es evalutate ab le puncto de vista de accurate mesurationes de dosage per via oral como etiam per via parenteral. Le declaration e le duration del effecto es mesurate, e omne symptomas de toxicitate es notate sin reguardo a si illos es renal, electrocardiographic o altere.

Es stipulate que nulle agente es qualificate como droga in le tractamento de hypertension si illo non satisface le sequente tres criterios: (1) Illo debe esser potente como agente antihypertensive. (2) Illo debe esser uniforme e predicibile in su effectos. (3) Illo debe posseder un basse toxicitate.

In le presente studio, tres drogas esseva investigate que es representantes del tres principal gruppos de agentes antihypertensive. WIN 8778 es un agente de blocage adrenergic. Le observation pharmacologic initial monstrava que illo es plus potente que Dibenzylina e etiam que illo es minus toxic. Ab le puncto de vista clinic il esseva constatate que illo produce angina, palpitation, tachycardia, e nervositate. Iste droga esseva potente. Su absorption oral esseva bon. Sed proque illo satisfaceva solmente duo del tres criterios, il esseva concludite que illo non es de valor in le tractamento de hypertension.

WIN 12.512–2 es un agente de blocage ganglionic. In studios laboratorial preliminar illo se monstrava superior a hexamethonium. In essayos con patientes hypertensive illo satisfaceva criterios un e tres, sed il esseva constatate que su absorption ab le vias gastrointestinal amontava a solmente 1 pro cento. Proque illo ha nulle avantage super le presentemente disponibile agentes de blocage ganglionic, su uso non es recommendate.

WIN 13.596–2 es un agente con proprietates de blocage central e etiam ganglionic. In animales laboratorial illo se monstrava potente como droga antihypertensive. Sed in patientes hypertensive illo effectuava un regular augmento del pression sanguinee. Proque le droga non satisfaceva le prime criterio, i.e. le criterio de potentia hypotensive, illo non esseva subjicite a investigationes additional.

Il es a sperar que le uso de iste technicas general in le evalutation de nove agentes antihypertensive resultara in le possibilitate de evalutar nove drogas plus prompte e efficacemente.

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THE TEACHING OF INTERNAL MEDICINE. THE EVALUATION OF LECTURES AND LECTURERS: A DISCUSSION OF RESULTS OF A STUDY BY FACULTY AND STUDENTS AT THE UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE *

By MAX SAMTER, M.D., F.A.C.P., MARK H. LEPPER, M.D., F.A.C.P., and MAX M. MONTGOMERY, M.D., F.A.C.P., *Chicago, Illinois*

INTRODUCTION

THE esteem with which medical educators have looked upon lectures has shown a considerable decline during the course of the past century. In their biography of William Henry Welch, for instance, Flexner and Flexner [1] write:

"Sometimes, however, the professors whose words were to be memorized possessed excellent scientific training; almost all had rounded out their inferior American medical education with periods in Europe under masters. Alonzo Clark, the professor of practice, had followed Bright and Louis in their hospital rounds. Welch remembered: 'He was the one that brought that new French medicine to this country in his early days, and was greatly interested in pathological anatomy.' Since Clark's lectures were 'supposed to be the embodiment of all the wisdome of the practice of medicine,' a set of notes on what he had said was considered the key to professional success; Welch was offered as much as a hundred dollars for the excellent set he had kept."

Yet in a recent report Turner and his associates [2] sharply limited the areas of instruction in which lectures might still be used:

"During recent years there has been a marked decrease in the amount of time devoted to the didactic lecture method of instruction in medical schools and a similarly marked increase in other methods of instruction designed to engage the active participation of the student. As now utilized by leaders in medical education, the lecture, where retained, is not an oral diarrheal repetition of the printed page but is designed to highlight advances, indicate differences of opinion and their possible resolution, and to correlate material with texts and other current literature. Small group and conference teaching has assumed a role of greater importance in general, and almost individual teacher-student relationships have become possible in many phases of instruction in the clinical fields."

* Received for publication January 17, 1955.
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Some of the reasons for the change are obvious. During Welch's training and during his early years as a teacher few comprehensive texts were available to medical students. The teacher's words were carefully recorded and handed down from generation to generation, while our age is fortunate in owning a wealth of books which cover the general and specialized aspects of the theory and practice of medicine. Since the same details which once were offered from the lecture podium can now readily be found on the printed page, one wonders whether lectures still serve a useful purpose in the curriculum of a medical school.

The present study attempts (1) to analyze the effectiveness of a series of lectures presented to the Junior class of the University of Illinois College of Medicine, and (2) to re-define their purpose in the light of our analysis.

In Spring, 1952, the third-year medical students of the University completed a questionnaire. The questionnaire was simple and encouraged an essay-type evaluation of the bedside training and didactic instruction which had been presented during the academic year. The class was articulate. More than 60% of the students favored "practical teaching"; more than 80% stated that lectures had been a waste of time and should be either improved or abolished.

The complaints of the students were specific. Five areas of failure were listed, in the following order:

1. Poor lecturing.
2. Poor timing, which failed to correlate didactic teaching with bedside experiences.
3. Incomplete coverage of several sections of internal medicine.
4. Emphasis on individual research and on areas of interest to the individual instructor, rather than emphasis on the field as a whole.
5. Imperfect instruction, with lack of contact between faculty and students.

It seemed to us that all but the first objection could be remedied by appropriate measures. The complaint of poor lecturing, on the other hand, is vague and does not lend itself to ready interpretation. In order to determine its meaning, a Committee was designated to survey lecturers and lectures, and to suggest methods for improvement. In essence, this paper represents a report of the Committee.

Experimental Procedure and Results

During the first year of the study, lectures in internal medicine were divided into 11 sections. A total of 68 hours were available, which were distributed as follows:

1. Cardiovascular and Renal Diseases	14 hours
2. Diseases of the Liver and Pancreas	4 hours
3. Gastrointestinal Disease	6 hours
4. Diseases of the Endocrine Glands	6 hours
5. Diseases of the Chest	8 hours
6. Infectious Diseases	7 hours
7. Diseases of Allergy	5 hours
8. Diseases of Muscles, Bones and Joints	5 hours
9. Hematology	5 hours
10. Diseases of Metabolism and Nutrition	4 hours
11. Preventive Medicine and Public Health	4 hours

Each section was controlled by a chairman, who either lectured himself or appointed the lecturers. Each chairman submitted to the Committee an outline of the material presented in each lecture. No attempt was made to advise the chairman on the contents of the lectures given by him or by his associates; it was felt that it was a prerogative of the lecturer to decide upon the adequate coverage of his field. Sections 2, 3, 4, 7, 9 and 10 were given by a single lecturer for each section; sections 1, 6, 8 and 11 were given by several lecturers; and in section 5 each lecture was given by a different lecturer. The lectures were held on Tuesday at 4:00 p.m. and on Friday at 8:00 a.m. Originally the Committee had planned to hold lectures at a uniform hour; the difference in time proved to be advantageous, however, because it permitted us to estimate the effect of the hour at which the lecture was given, upon attendance.

Selection of Lecturers: In its evaluation the Committee selected lecturers who were distinguished by a well defined and characteristic manner of presentation. The generous coöperation of our lecturers in an experiment which encouraged students to submit a critical review of their performance is gratefully acknowledged.

The lecturers differed widely. Lecturer A gave a polished lecture. He presented broad concepts, and omitted detail, but held the attention of the audience by inserting many illustrative stories based on his personal experience.

Lecturer B followed a rigid outline. A strongly systematic lecturer, he was supported by excellent visual aids; he had a tendency, however, to disrupt the attention of his audience by many mannerisms in speech and gesture.

Lecturer C had been a lecturer for many years. Like lecturer B, he adhered to a prepared framework but enlivened it by frequent clinical reflections. He gave considerable attention to detail, but limited his visual aids to blackboard drawings of moderate effectiveness. He was intolerant to late comers and interrupted his lectures on several occasions to draw attention to stragglers. His voice was soft but carried well after he was persuaded to use a microphone.

Lecturer D presented the same subject matter as lecturer C. The elegance of his presentation and his clever change in emphasis made it appear as if he presented broad lines of thought, whereas close analysis showed that his lectures included approximately as much detail as those of lecturer C. His visual aids were well selected and were used to summarize the contents of the lecture at the end of the hour.

Lecturer E presented an unpopular field. His delivery was dry and monotonous. He presented his material in concentrated blocks. He leaned heavily on statistics. He had little, if any, sense of humor. Each of his answers to questions from the audience was again a small lecture; he had no ability for give and take, yet there was no doubt about his competence.

Lecturer F paid little attention to detail but, like lecturer A, used his personal experience to clarify the practical significance of his concepts. His voice was adequate—perhaps too loud. He made extensive use of the blackboard but failed to exhaust the opportunities for visual aids.

Evaluation of the effectiveness of the series of lectures demanded the evaluation of both methods and results of instruction. It required an appraisal of (1) faculty by faculty; (2) faculty by students. In addition a more objective appraisal was arrived at by analysis of the record of attendance and a study of the results of special examinations.

Method of Evaluation of Faculty by Faculty. The form used by faculty members in the evaluation of lectures is reproduced in table 1. It provides space for the analysis of (1) the students' response to the lecturer, and (2) the adequacy of the lecture. The evaluation of the lecture was divided into (a) general information, including an abstract of its contents; and (b) specific questions about [1] preparation, [2] organization, and [3] presentation, the last amplified by a sub-question on the adequacy of the lecturer's voice and on his use of visual aids.

A point system was used in the analysis of preparation, organization and

TABLE 1

Lectures in Medicine

Group: Lecture No. Date: Hour:

Lecturer:

Students' Response:

Attendance:

Attention:

Types of Questions Asked:

Attempts to clarify:

Attempts to supplement:

Lecture:

Content (Outline in brief):

Preparation:

Organization:

Presentation:

Adequacy of Voice:

Visual Aids (e.g., use of blackboard for infrequent or complicated terms? slides? demonstration of patients?):

Remarks:

Initial———

presentation of each lecture. A minimum of one point, for poor performance, and a maximum of 10 points, for excellence, were awarded in each category. Since each of the lecturers included in the study was judged by three faculty members, each instructor had a range from a minimum of three points to a maximum of 30 points in each category.

Results of Evaluation of Faculty by Faculty. Faculty members were present and recorded the entire series of lectures during the Junior year, but only the six lectures which were evaluated simultaneously by faculty and students are included in this study. The forms of the three faculty members were, as a rule, in good agreement, although individual procedure differed on occasion. In the evaluation of attendance, for instance, some members of the faculty reported a general impression, while others actually counted

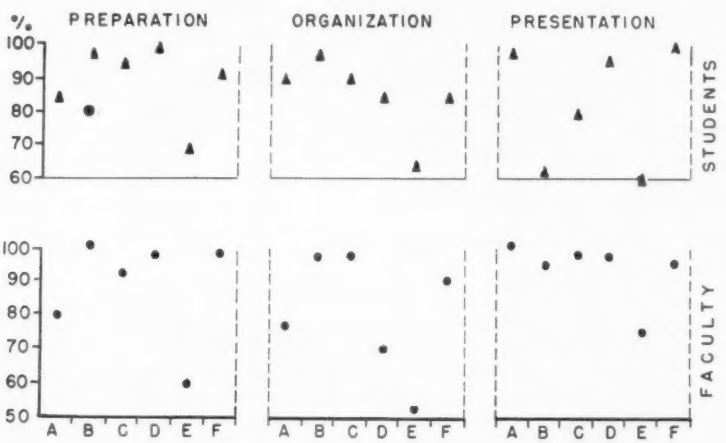

FIG. 1. Comparison of scores (in percentages of the maximal obtainable score awarded to six selected instructors for preparation, organization and presentation of their lecture, (1) by faculty, (2) by students.

and compared the number of students who were patently asleep during the first part and during the last part of the lecture. Each of the forms completed by faculty members contained an outline of the content of the lecture. It could be readily seen that content was of primary importance to the members of the faculty, since about four fifths of all comments related to this subject. The faculty's judgment of the preparation, organization and presentation of the lectures is summarized in the lower half of figure 1. The figure records the percentage of the possible maximum the lecturer reached in each of the categories during the lecture under study.

Shortly after the beginning of the study it became obvious that the question of preparation should not have been included in the forms. Although the graph (figure 1) shows apparent agreement between faculty and students,

the lack of comments suggested that it was treated lightly, probably because preparation is difficult to assess and because the members of the faculty assumed, charitably, that even poor lecturers must have spent some time in preparing their lectures. Organization, on the other hand, was given a great deal of attention. Interestingly enough, organization in the minds of the faculty appeared to be synonymous with adequacy of content. This is important, because it differs decidedly from the students' interpretation. Presentation was judged by fairly uniform standards, particularly since the subdivision of the question called attention to specific points. Distracting habits and undesirable mannerisms were recorded with equal faithfulness by faculty and students.

Method of Evaluation of Faculty by Students. The form designed for the students was almost identical with the form designed for use by members of the faculty but had one important addition: a space for a personal code in the upper right corner of the form. The code consisted of three parts: (1) a code word selected by the student and entered on each consecutive form throughout the year; (2) the student's age, and (3) his standing in the upper, middle or lower third of the class.

Analysis of the forms submitted by the students was similar to the analysis of the forms completed by members of the faculty, but the requirements for judgment were less elaborate. Preparation, organization and presentation were judged either poor, good or excellent. A poor performance was credited with two points, a good performance with four points, an excellent performance with six points, in each category; on occasion, intermediate numbers (3 or 5) were used in an attempt to reflect a student's opinion as accurately as possible. If 100 students attended a particular lecture the instructor could obtain a maximum of 600 points each for preparation, organization and presentation.

Results of Evaluation of Faculty by Students. The forms were completed by the students during the latter part or at the end of the lecture. Students were reluctant to express definite opinions about the performance of the faculty; in spite of the anonymity, it was not possible to obtain score sheets from the entire class. The number of forms that were returned ranged from 96 to 142, and averaged 114.

Approximately 60% of the students did not bother to complete the outline of the content of the lectures, presumably because they were preoccupied with taking their notes; of those who complied, the majority gave only the general topic with one or two words, e.g., "leukemia, acute and chronic."

Comments were abundant and were strongly complimentary ("Wish we had more lecturers like him"), or strongly critical ("Why doesn't he write some stuff on the blackboard?"). Some comments were amusing, like the one from the student who compared lecturer A and lecturer B: "Lecturer A is like reading a novel; lecturer B, a telephone book. I prefer lecturer A, but who can get telephone numbers from a novel?" The major

complaints were: (1) excessive speed, and (2) difficulty in taking notes, even when the superior quality of the lecture was acknowledged.

The score that the students awarded for preparation, organization and presentation is summarized in the upper half of figure 1.

The graph seems to indicate a striking similarity between the judgment of the faculty and the judgment of the students. The similarity is true, however, only in part. Questioning of individuals made it evident that the attitudes toward the grading of preparation were the same among faculty and students. Organization, on the other hand, meant for the majority of the students that material was presented in a manner which made it possible to take notes. The students awarded, as a whole, higher grades for organization than did the faculty, perhaps because they were less critical of content. Lecturer A, for instance, in the estimation of the faculty reached only slightly more than 75% of the maximum, whereas he was awarded 90% of the maximum by the students. The faculty gave lecturer D 70% of the maximum for organization; the students, 86%. Lecturer E was credited with 55% of the maximum rating by the faculty, with 65% by the students.

Poor presentation disturbed the members of the faculty less than it disturbed the students. Lecturer B, who presented a well organized lecture, received a faculty rating of 90% of the maximum for presentation, whereas the students gave him a rating of only 65%, in spite of the fact that he illustrated his lectures with attractive slides.

To our surprise, outstanding presentation failed—with one possible exception—to influence the rating of organization. Presentation, on the other hand, appeared to be essential for student acceptance. The two instructors who won the annual instructorship awards received the highest rate for presentation, not for organization of their lectures.

A breakdown of the returns according to the class standing revealed only insignificant differences. Intelligent comments were found in each third of the class. The majority of the comments did not differ appreciably among the three groups, but there appeared to be a shift of emphasis from organization to presentation in the upper third of the class.

R. S. Jones,[3] who reviewed our findings, emphasized the fact that students' ratings of teachers are influenced by a variety of complex factors, which include previous experiences in school, total school organization, attitudes about particular subjects, ability and the like. Moreover, psychologic research has substantiated, in teacher-student relationships, the presence of a "halo effect," which accepts the superiority of the teacher as a foregone conclusion. A. S. Barr and others[4] have pointed out that this effect complicates the rating of teachers and is a significant source of error in rating. The total of the returns in our study made it possible to examine the question whether certain types of lecturers appeal to certain types of students. Table 2 lists, in the first column, the number of students who recorded a favorable opinion about their instructor; in the second column,

TABLE 2

	Favorable	Unfavorable
A	88	28
B	72	70
C	74	30
D	92	26
E	48	48
F	84	24

the number of students who recorded an unfavorable opinion. It can be readily seen that lecturer D had the most favorable ratio between approving and disapproving opinions, whereas the ratio of lecturers B and E approximates one to one. Closer analysis of the forms shows that 64 of the 72 students who approved lecturer B also approved lecturer C, who had similar traits; on the other hand, the majority of the students who disapproved of lecturer A also disapproved of lecturers D and F, and a small but significant number of students appeared to disapprove of all lecturers. However, if a lecturer's performance fell sharply below the general level of adequacy, the relatively clear lines of demarcation between the approving and disapproving groups became obscured.

Evaluation of Lectures by Analysis of Student Attendance. Attendance at the lectures was *voluntary*. The students were assured that the Department would not call roll and that absence from lectures would not be held against them, but that material presented in lectures was likely to be included in their final examinations. In introductory remarks it was pointed out that an occasional individual might not be suited to learn from lectures and might derive considerably more benefit from intensive study of textbooks.

Attendance was recorded by the faculty members who were present at the lectures. The figures represent an actual count during the middle of the lecture. The attendance before (1952–53) and after (1953–54) reorganization of the lecture course was analyzed.

The number of the students attending each lecture in the 1952–53 session is shown in figure 2. The figure shows (a) the attendance at 4:00 p.m. (unbroken line) lectures, and (b) the attendance at 8:00 a.m. (broken line) lectures. The series is divided into (a) the 11 sections of the course, and (b) the three quarters, each separated from the other by one week's vacation. Attendance ranged from 90 to 160. Although it did not fall below 90 at any time, the possible maximum of 166 was never reached. An analysis of the graphs indicates that each quarter began with a high attendance. This was particularly true for the Fall quarter, during which attendance remained relatively stable. Toward the end of each quarter attendance fell; even a superior instructor attracted more students at the beginning of the year than during the latter part of the winter. The average attendance of the afternoon lectures during the Fall quarter was 145; during the Winter quarter, 133; during the Spring quarter, 127; of the morning lectures during the Fall quarter, 127; Winter quarter, 119; Spring quarter, 111.

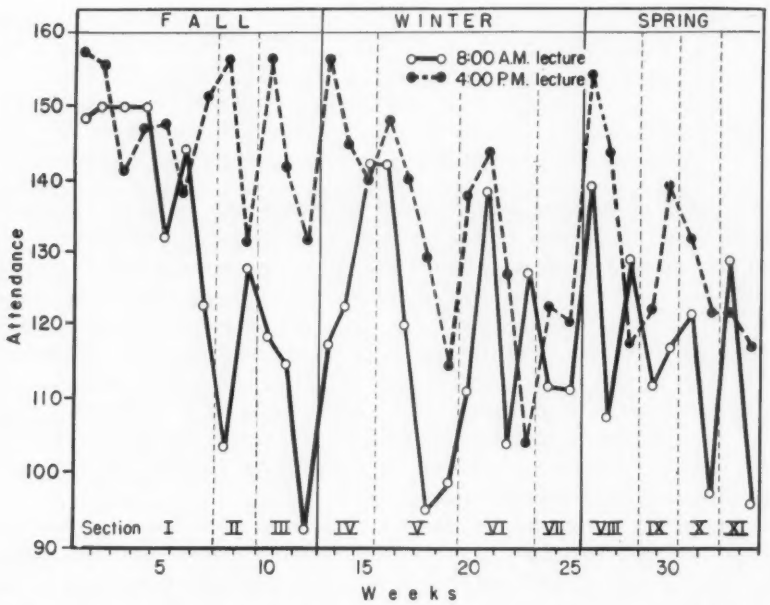

FIG. 2. Attendance of the Junior class at lectures in Medicine presented during the year 1952–53 at 8:00 a.m. and 4:00 p.m. (Total number of students in the Junior class, 166.)

The general trend which was apparent in each of the quarters was broken by specific trends which apparently reflected the attractiveness of the lectures. Attendance revealed interest in, not necessarily quality of, instruction. The eight lectures in the fifth section, for instance, illustrated this response. The lectures were presented by seven individual instructors who had not been in touch with each other and who offered valuable but nonintegrated lectures. Accordingly, attendance fell below the usual level, recovered slowly during the subsequent section, then decreased again toward the end of the quarter. The lectures held during the seventh week of the Fall quarter illustrate this point further. The Tuesday afternoon lecture was poor because the lecturer discussed a new field in a hesitant and inadequate manner. His failure is reflected in the Friday morning lecture which followed and showed a sharp decrease in attendance. In other words, the attendance at any instructor's lecture depended in part on the performance of the lecturer who preceded him.

Attendance at noncompulsory lectures is a sensitive indicator of:

1. Distracting environmental factors, e.g., weather conditions.
2. Pressure of term examinations.
3. The student's interest in the course.

The graph makes it evident that the attendance at 8:00 o'clock lectures is a much more sensitive indicator of the attractiveness of teaching than the attendance at 4:00 o'clock lectures. At 8:00 o'clock in the morning the student has to make a special effort to be at the University on time and to attend the lecture. At 4:00 o'clock in the afternoon he is already at the University, and it is much less of an effort for him to attend the day's final lecture.

While we are aware that several variables may influence the attendance of lectures on any given day, we believe that the influence of these variables can usually be established and that the interpretation of our data as an indicator of the student's interest in the course remains valid.

During the second year of the study (1953–54) the Committee reorganized the course in several ways. The following steps were taken.

1. During the Spring quarter of the (preceding) sophomore year the Department presented a series of orientation lectures, which outlined the transition from preclinical to clinical instruction and underscored the necessary changes in the student's approach to learning.

2. The sections were redistributed in an attempt to allow young and relatively inexperienced members of the teaching faculty to teach during periods of expected high attendance, and experienced lecturers during the more critical periods at the end of quarters.

3. The lectures on public health and preventive medicine, which had been previously given as a block toward the end of the academic year, were replaced by panels. At the conclusion of each of the 11 sections, instructors of the Department of Medicine and of the Department of Preventive Medicine and Public Health discussed jointly the problems of prevention pertinent to each.*

4. The Department divided the class into groups of 15 students each, who met, during the Spring quarter, with the instructors of each section for informal discussion of the presented material.

5. In coöperation with Professor T. S. Jones, head of the Department of Illustration, we reviewed our visual-auditory equipment and found it wanting. The Committee issued an invitation to the teaching staff to submit their slides and other visual material to Mr. Jones prior to presentation for comment and suggestions. In addition, the College of Medicine installed in its major lecture auditoriums dim-out switches which permitted the projection of lantern slides in a half-light rather than in complete darkness, which had been observed to disrupt the continuity of the lecture and to be followed by a lengthy period of gradual recovery.

* In spite of the elimination of the lectures on public health and preventive medicine, the number of sections remained the same, as a result of the addition of a section on parasitology and tropical medicine.

Results

The number of students who attended each lecture in the 1953–54 session is shown in figure 3. The figure records the rearrangement of the lecture series. During the Fall quarter the students had, as before, two lectures each week, one at 4:00 p.m., the other at 8:00 a.m. During each week of the Winter Quarter the students had three lectures, two at 8:00 a.m., one at 4:00 p.m. The figure also indicates the occasional panels on

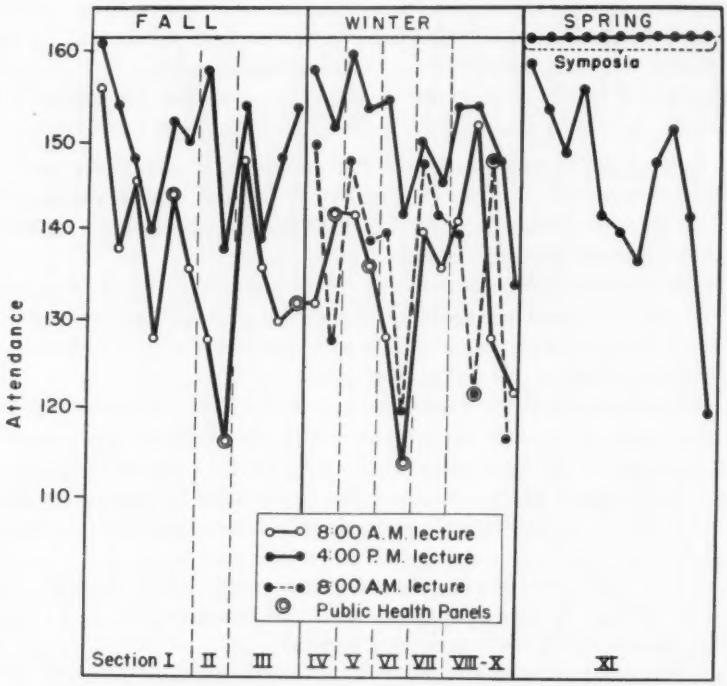

Fig. 3. Attendance of the Junior class at lectures in Medicine presented during the year 1953–54 at 8:00 a.m. and 4:00 p.m. Symposia held at 8:00 a.m. during the Spring quarter were compulsory. (Total number of students in the Junior class, 166.)

public health and preventive medicine and the symposia between individual instructors and small sections of the class which replaced the morning lectures during the Spring quarter. The symposia were compulsory and therefore not included in the evaluation of attendance.

The graph shows that attendance ranged from 161 in the beginning of the academic year to 114 on a winter morning. Average attendance during the afternoon lectures was 149; during the morning lectures, 136. In contrast to the preceding year, the variation between quarters was negligible:

average attendance during the afternoon lectures in the Fall quarter was 149; in the Spring quarter, 145. The same general and specific trends which distinguished the previous graph (figure 2) can still be recognized, but the over-all increase in interest clearly outweighs the other variables.

The Committee is aware of the fact that the apparent improvement in the attractiveness of the course has been accomplished by a considerable effort. Whether less comprehensive measures would have been adequate remains to be seen in future years. Whether the effort is justified depends on the rôle assigned to lecturers within the larger framework of the clinical curriculum as a whole, a decision for which this study furnished preparatory material but which was not its primary concern.

Evaluation of Lecturer by Results of Examinations. In 1951 the Department of Medicine changed from the essay type to a multiple choice type of examination. Questions were submitted by the individual instructors in the course and cleared through an adhoc committee of five members of the Department of Medicine. The examination was held at the end of the academic year. It consisted of 40 questions; two hours were allowed for the completion of the examination.

In 1952 and 1953 the Committee decided to make the final examination part of its survey of the effectiveness of lectures. The Committee enlarged the final examination to a total of 50 questions. Of the 50 questions, 10 were designed by the Committee to clarify specific problems under investigation. Samples of questions selected by the Committee and the percentage of correct answers in the upper third and in the lower third of the Junior class are summarized in table 3. The exact wording of the questions is listed in Appendix I.

Some of the questions (1a, b, c, and 2) attempt to establish the degree of repetition and of emphasis which is necessary to convey a certain amount of information to the Junior class; others (questions 3 and 4) test the importance of visual aids for the upper and lower third of the group. One question (5) was specifically designed to test the effectiveness of our instruction in electrocardiography, then under debate. Other questions attempt to establish the familiarity of students with research in progress (6); the teaching value of mimeographed material (7); the usefulness of a matching question as an estimate of a student's knowledge (8); the comparative ability to recognize a common syndrome (9) and a rare disease (10) which had been discussed at approximately the same length during the lecture series—the latter, however, complicated by a historical disguise; and, finally, the effect of the wording (11 and 12) on the ability of the upper and lower third of the class to give correct answers.

The test questions confirm the impression that the upper third of the class has a better ability to accept and to reproduce marginal material presented in lectures. Accordingly, repetition as a tool of instruction was more important for the lower than for the upper third of the class. This,

TABLE 3

	Percentage of Correct Answers	
	Upper Third of Class	Lower Third of Class
*1. Minor subject casually mentioned		
a. Once	38	8
b. Twice	68	38
c. Three times	72	64
2. Minor subject emphasized	70	58
3. Minor subject without visual aid	58	24
4. Minor subject with visual aid	74	64
5. Interpretation of electrocardiogram	78	44
†6. Question on research in progress	82	38
7. Question based on mimeographed material	84	58
8. Matching question	98	88
9. Question on well defined clinical syndrome	92	86
10. Question on rare disease	44	12
11. Coombs' test question—suggestive wording	82	49
12. Coombs' test question—deceptive wording	76	31

* This question was included, with minor variations in wording, in the final examinations of three consecutive years.

† At the time of the examination the treatment of acquired hemolytic anemia with ACTH or cortisone was not the accepted treatment, but was under investigation in the Department of Medicine and in other departments of medicine throughout the country.

of course, is not surprising, and is in accordance with Steen and James'[5] observation that the more able students profit more from the lecture method than do the less able students. The value of visual aids in the upper third of the class was approximately the same as the value of one repetition; in the lower third they were twice as important. Mimeographed material was retained by 84% of the students in the upper third of the class but by only 59% of the students in the lower third. Seventy-eight per cent of the upper third of the class, and only 44% of the lower, recognized an essentially normal electrocardiogram. In both years questions on familiar technics, or on common or typical syndromes, or on subjects which had been taught with effort and emphasis, were answered equally well by both groups. The differences between the upper third and lower third which were obscured by questions in familiar areas were brought into sharp focus when questions were concerned with marginal information, e.g., with less common diseases or with research in progress. It is this type of question which, as one of the instructors remarked, "separates the men from the boys."

The information obtained by the Committee from test questions of this type, which were graded but not included in the students' records, has been valuable but limited. The official grades on the recorded part of the examination, which consisted of 40 questions submitted by instructors, showed a range of correct answers from 56% to 89%. The evaluation of the Committee's 10 test questions in 1951 revealed that in the lower third of the class the percentage of correct answers was 49; in the upper third, approximately 78. While these numerical results of the Committee's tests support the statistical validity of our examination as a yardstick of the student's class standing, they fail to shed much light on the basic problem of the study: whether lectures, if properly designed and executed, can convey a predetermined and reproducible amount of medical information to an audience of widely varied capacity.

Material taught in lectures can be roughly divided into (1) obligatory knowledge that must be taught to and remembered by the entire class, and (2) incidental information that, whatever its importance, can be readily found, and understood, once the fundamental concepts of disease are known. Our data point to specific deficiencies in our methods of teaching but do not distinguish between the competence of the instructor on the one hand, and the competence of the student on the other.

At the end of the second year of the study the Committee attempted to compare the instructor's opinion of the importance of, and his emphasis on, a given subject with the grades of the Junior class which reflected in the field of his particular interest. The experiment was carried out in the following manner. The Committee prepared an abstract which outlined the tentative conclusions of our studies. The Committee requested questions for the final examination from its faculty. In keeping with its original policy, the Committee left to its instructors the decision as to what constitutes obligatory, and what incidental, knowledge. We insisted on technical uniformity of the questions but did not alter either wording or content. After approval by a subcommittee, as before, the questions were returned to the individual instructors with a copy of the abstract and with the request that they divide the examination into (1) questions which must be correctly answered by the entire class, and (2) questions which are expected to be answered by ———% of the upper third of the class, by ———% of the lower third. In addition, Committee members who had attended the lectures contributed their own estimate of the expected outcome.

We have summarized expected and actual grades for four of our questions in table 4. It is obvious that any member of a junior class in medical school should be able to answer the first of the four questions; in fact, at the conclusion of the examination, when the Junior class met with the Committee to review the examination, the reading of this particular question was greeted with considerable hilarity.

TABLE 4

		Instructor's Estimate	Committee's Estimate	Actual Results
1. Another term for cholangiolitic cirrhosis is: a. Portal cirrhosis b. Tropical cirrhosis c. Laennec's cirrhosis d. Biliary cirrhosis	Upper third	100	100	100
	Lower third	100	100	100
2. A 20 year old male patient complains of cough, expectoration, fatigue, fever and loss of weight for three months. Physical examination reveals loud moist râles in the left apex. Tuberculin test is negative. X-ray reveals a 6 cm. cavity in the left apex. Before any more diagnostic work is done, which of the following is the most likely diagnosis? a. Coccidioidomycosis b. Lung abscess c. Histoplasmosis d. Tuberculosis e. Carcinoma	Upper third	90	85	74
	Lower third	70	70	44
3. A 45 year old man with epigastric pain is found after adequate x-ray study to have a gastric ulcer. A competent gastroscopic examination is then performed. The opinions of the radiologist and the gastroscopist differ; one states that he believes the lesion to be benign, and the other states it is malignant. You should advise: a. Repeated x-ray and gastroscopic examinations b. Gastric analysis with histamine c. Therapeutic test d. Prompt surgery e. Cytologic study of the sediment	Upper third	95	95	74
	Lower third	75	85	44
4. A 31 year old Negro woman has had a slight normocytic anemia for a long time. Several other members of the family are known to have had slight to moderate anemia. A sickle-cell preparation fails to reveal any sickling tendency. Numerous target cells are evident. A blood sample is sent for abnormal hemoglobin detection. If any abnormal hemoglobins are shown to be present, which is the most likely: a. Type A b. Type S c. Type C d. Methemoglobin	Upper third	70	75	69
	Lower third	40	35	29

The second question failed to fulfill the instructor's expectations and made it evident that the differential diagnostic problems which it outlines need further clarification. The third question was on a subject of considerable importance to the instructor—surgical treatment of a suspected gastric lesion. The answers suggest either inadequate presentation, or the exposure, perhaps at the bedside, to other instructors who might have reasoned differently in a controversial issue of this type. Interestingly enough, the instructor apparently convinced the Committee member, who, familiar with his attitudes, might have listened with preconceived ideas. The fourth question covers marginal material; in this instance the estimates of instructor and Committee are in fair agreement with the results of the examination.

We plan to repeat the study at the end of the current year on a larger scale and to subject its results to statistical analysis; at this time it is included here as a basis for discussion rather than as a suggested experimental approach. Our limited experience, however, warrants the hope that this relatively simple device will ascertain (1) what the lecturer meant to accomplish, and (2) what he has actually accomplished; and thus form an acceptable index of the adequacy of his teaching.

The Committee recognizes that, as time goes on, it will be confronted with other problems. So far, for instance, our test questions have failed to make allowances for the length of time elapsed between the date of presentation of the material and the date of examination. The duration of recall, which should be one of the determining factors in selecting teaching methods, has received little attention in educational research. Corey [6] suggested that reading produces slightly greater immediate recall than presentation of the same material in lectures, but that delayed recall showed little, if any, difference between the two methods of learning. Jayne [7] found that lectures are superior in immediate recall to a silent movie, but that they are also more easily forgotten; yet the significance of these observations has yet to be established. The Committee feels that a systematic study of the duration of recall is needed.

When in recent pilot studies we prepared questions based on the lectures of the preceding year, we found evidence that such material is not only more easily accepted but also more adequately retained by the upper third than by the lower third of the Junior class.

Conclusions

As our study has progressed we have become increasingly aware of the complexity of our task. A paragraph from the Encyclopedia of Educational Research summarizes its problems:

"A major weakness in research concerned with methods of teaching lies in the confusion of educational theory in accordance with which results have been interpreted. Many studies have sought to discover, for example, superior procedures for

accomplishing goals of subject-matter mastery while giving little or no consideration to the effect of the method of attaining such goals upon the total growth of the pupil. A second limitation has been the inadequacy of research instruments and techniques available. Experimental research has not frequently produced findings of high validity because of the complexity of the experimental factor, in some cases involving curriculum reorganization; the control of non-experimental factors, especially teacher skill, zeal, and enthusiasm, is seldom adequate; the measurement of the outcomes of instruction is rarely satisfactory and often is in terms of extraneous purposes; and the period of experimentation is usually not long enough for the pupils and teacher to become adjusted to a new method. The tendency to measure the effectiveness of teaching in terms of outcomes which can be measured by verbal responses of pupils represents, perhaps, a third impediment to research concerned with methods of teaching."

In spite of the difficulties, we feel that we are entitled to a number of tentative conclusions:

A. Lecturers. Analysis of our records makes it clear that only part of an instructor's performance can be judged objectively. Preparation and organization are prerequisites of good teaching, but do not alone make a good teacher. Instructors who have organized their material in virtually flawless form were judged inferior to others who accomplished, consciously or unconsciously, identification with the group by the manner of their presentation. Contact of this type may include, but is not necessarily based on, showmanship. It is, as one of our students expressed it, "the ability to make one feel that the teacher speaks directly to you."

Lecturers vary. The Committee has become aware of the power of the capable lecturer who may have an extraordinary impact on young minds in the formative state—as Osler said: "Nothing is as iridescent and long lasting as a bubble blown by a successful teacher." Yet the Committee felt that a student (who has to learn to handle all kinds of patients) must learn to accept information from teachers who are not to his individual liking. At the same time the Committee realized that much remains to be done to convince teachers that the ability to establish contact with students is not a mystical quality. The use of proper visual and auditory aids, of repetition and emphasis, and, more than anything else, a careful analysis of the specific needs of the audience to which a particular lecture is addressed, has brought reassuring results and great satisfaction to teachers who were made, not born.

B. Students. Whether students like or dislike lectures is difficult to ascertain. Our students seem to prefer anonymity, and hesitate to be counted on questions which they consider controversial. Luderman [8] revealed that students rated lectures as the best "ground-covering technique"; and Meyer,[9] that the rating of teaching methods and of instructors by students is bound to be influenced by the type of test which they anticipate. The analysis of our test questions makes it likely that the means of instruc-

tion that are suitable for the upper third of the class might not be adequate for the lower third, which is, of course, the cause of our concern. In general, it appears that students in the upper third and in part of the middle third of the class, if properly motivated and orientated, are able to select methods of learning that are suitable for their particular needs; but that considerable effort is needed to assure effective teaching of the less resourceful lower third of the group. The test questions also confirm that the lower third needs more repetition and more visual aids than the upper third. This is a serious problem, because the demands of the lower third are bound to slow down the progress of the more capable students in the class.

The breakdown of the code responses indicates that a significant segment of the students will produce foreseeable responses to a particular lecturer. The reasons for this selectivity are not well understood; they apparently depend on various elusive factors, e.g., on constitutional makeup and childhood experiences. In each generation of students we find a number of individuals who refrain from taking notes because they "cannot get anything out of them." In *A Study of Imagery in Research Scientists* Roe [10] concluded:

> "It would seem, then, that there are differences in mode of thinking which may be somehow related to socioeconomic background, and which are related to vocation and to certain aspects of test performances.
>
> "My data offer no information on why subjects have come to rely on some modes of thinking rather than others. Whether there is a hereditary factor, as Galton suggested, or whether it is largely training or experience, and if so how early and by what means the mode is set and how changeable it is are unsolved but fascinating problems. As to manner or cause of development, leads might be obtained from cultural anthropology as well as from case histories, as has been done here. The association with test performance, suggested here, could be easily pursued. The vocational aspect also warrants further investigation, with particular regard to its implications for training."

It might well be that this author's experience applies to the teaching of medical students.

It seems most difficult for our students to shed the habits they acquired in grade school, high school and college, and to replace their apprehension by the relaxed recognition that grades represent only one of the yardsticks —and, in this Committee's opinion, probably not the most important one— of their development.

C. Lectures. The scope of lectures in the curriculum of our medical school needs careful reëxamination. Lectures can guide, direct, convey broad outlines, and encourage students to search additional information; their effectiveness in teaching detail varies with the class standing. Bright students are apparently able to learn detail in lectures.[3] In fact, Remmer,[11] who compared the test performance of three groups: (a) a large lecture section, (b) large lecture plus small recitation sections, (c) small quiz

sections, found little superiority of any one method over the others; and Longstaff,[12] in similar experiments, arrived at essentially the same conclusions. It is evident, however, that the scope of lectures differs in different years of medical training. Freshmen and sophomores need stimulation; juniors need a firm framework of concepts; and seniors, a sufficiently critical review of the third-year material to realize that facts, as facts, are meaningless unless they are weighed and viewed in proper perspective.

The technic of lecturers requires increasing attention; the recognition that the Junior class is not a uniform group, but has a wide range not only of intellectual ability but also of its pattern of perception, makes it imperative to use a multicolored approach to achieve the broadest possible pattern of presentation.

The question of whether lectures have a place in the clinical curriculum of a medical school has been hotly debated. The present study does not attempt to enter the controversy. The Committee has been concerned with the improvement of lectures as they exist. The issue of whether the same material could be taught as effectively or better at the bedside, in seminars or in conferences would have to be decided by comparing the effectiveness of lectures with the effectiveness of other teaching media by the same objective methods which we have instituted at the University of Illinois. Pilot studies of this type have been carried out by Kahn [13] in college biology, and by Edmiston and Braddock [14] in social studies, but not, so far as we were able to ascertain, in the teaching of medicine.

As long as the four-year curriculum of the medical school is maintained, it seems likely that the increasing mass of information cannot be taught at the bedside or in seminars alone if we intend to keep the students abreast of current developments and progress. Our own conclusions resemble those of Welch, who was brought up on lectures and then advocated strongly the teaching in the laboratory and at the bedside; but toward the end of his life seems to have reached a compromise which restored, at least in part, lectures to their proper place:

> "Some important subjects, of course, 'either for lack of time or from the nature of the subject-matter, cannot readily be taught in the laboratory. The attention of the student in the laboratory is likely to be concentrated upon isolated facts . . . while other groups of facts and particularly broad general principles are in danger of being lost to view. There is, therefore, risk of loss of perspective in relying solely upon instruction in the laboratory.' For these reasons Welch would supplement laboratory work by didactic and demonstrative lectures." [1]

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Appendix I

1. Dyspnea, according to Cournand, will develop when the breathing reserve decreases below:

   a. 90 to 80% of normal
   b. 70 to 60% of normal
   c. 50% of normal
   d. 40 to 30% of normal

2. In the treatment of bronchial asthma, one of the following groups of drugs is contraindicated at all times and under any circumstances:

   a. Analgesics, such as acetylsalicylic acid
   b. Aminophylline and other xanthine derivatives
   c. Morphine and morphine derivatives
   d. Sympathomimetic drugs

3. The characteristic cell of the bone marrow in multiple myeloma is:

   a. Immature megakaryocyte
   b. Reticulum cell
   c. Immature lymphocyte
   d. Mature lymphocyte
   e. Myeloblast
   f. Plasma cell

4. (Same as No. 3)

5. The usual cause of a Q wave in Lead III is:

   a. Anterior infarct
   b. Posterior infarct
   c. Horizontal position of the heart
   d. Vertical position of the heart
   e. Clockwise rotation of the heart

6. A 30 year old Scandinavian woman has had sudden onset of fatigue, pale yellowish skin coloration, dyspnea on exertion, and low grade fever. There is no history of other recent disease or of drug or chemical exposure, and no family history of similar disease. No lymph nodes or abdominal organs are palpable. Icterus index is 25 units; cephalin flocculation, negative; red blood cells, 2.5 million; white blood cells, 15,000 per cubic millimeter; hematocrit, 21%; hemoglobin, 7.0 gm.; differential shows 6% stabs, 61% polymorphonuclears, 2% monocytes, and 31% lymphocytes. Peripheral smear shows some anisocytosis and spherocytosis, adequate platelets, and toxic granulation of neutrophils. The direct Coombs' test is positive; reticulocyte count is 4.5%; bone marrow is normoblastic. The initial treatment of choice is:

   a. Ferrous sulfate
   b. Splenectomy
   c. Cortisone or ACTH
   d. Vitamin B_{12} or liver extract
   e. Folic acid

7. In a patient with meningitis in whom spinal fluid examination revealed 7,000 cells per cubic millimeter, 15 mg. of sugar per 100 ml., and 210 mg. of protein per 100 ml., the occurrence of polyarthritis would make which of the following the most likely diagnosis:

   a. Pneumococcic meningitis
   b. Tuberculous meningitis
   c. Leptospirosis
   d. Meningococcic meningitis
   e. Meningitis caused by *Hemophilus influenzae*

8. A 40 year old white female complains of dyspnea and weakness which has been present for 24 hours. Match the symptom or sign from the list below with the disease which is most likely to accompany it by designating both with the same number:

1. A red throat with exudate which is wiped off	( ) Pneumococcic pneumonia
2. A pleural rub over the region of the right lower lobe	( ) Primary atypical pneumonia
3. A persistent, unproductive cough	( ) Influenza
4. No abnormalities on physical examination except fever and tachycardia	( ) Diphtheria
5. The dyspnea is extreme, requiring accessory muscles of respiration, and the lungs remain normal on physical examination	( ) Streptococcic sore throat

9. A 22 year old man presented a history of a serous urethritis followed in one week by a transient conjunctivitis and a few days later by an acute arthritis of a single joint, the left knee. The urethral discharge was said to have shown no intracellular gram-negative diplococci. The patient was acutely ill, with a temperature reaching 103° F. every day. There was no chill at the onset of the arthritis. The most probable diagnosis is:

   a. Atypical rheumatoid arthritis
   b. Acute gonorrheal arthritis
   c. Acute gouty arthritis
   d. Reiter's syndrome

10. Myxedema circumscriptum is occasionally found in the following condition:

   a. Sheehan's syndrome
   b. Cushing's disease
   c. Graves's disease
   d. Gull's disease
   e. Addison's disease

11. Anti-human globulin rabbit serum is used in:

   a. The diagnosis of lupus erythematosus
   b. Widal's reaction
   c. The typing of Rh factors
   d. The Coombs' test
   e. Tests for heterophil antibodies

12. The Coombs' test makes use of:

   a. Anti-human-red-cell rabbit serum
   b. Anti-rabbit-red-cell human serum
   c. Anti-human-globulin rabbit serum
   d. Anti-rabbit-globulin human serum
   e. Type-specific human agglutinins

SUMMARIO IN INTERLINGUA

Iste articulo analysa le efficacia del discursos oral presentate al studentes del tertie anno (*college junior class*) al Schola de Medicina del Universitate Illinois. Le studio describe plure (subjective e objective) manieras de tractar le problema. Un estimation subjective esseva obtenite per medio de questionarios executate per membros del facultate e per le studentes durante o immediatemente post un gruppo seligite de discursos oral. Methodos objective includeva le examine del valor de statisticas de "presentia e absentia" como indice del qualitates attractive de discursos

oral. Lor efficacia pedagogic esseva determinate in examines final que esseva preparate specificamente pro mesurar le capacitate de studentes in varie stratos de qualification de rememorar se datos e factos explicate a illes con varie grados de emphase. Le resultatos obtenite in le diverse subdivisiones del studio es summarisate, e conclusiones provisori es formulate in re le valor de discursos oral como instrumento pedagogic pro studentes de varie capabilitates. Plus que preparation e organisation es requirite ab le docente si on vole que ille establi le plus efficace forma de contacto con su studentes. Le modo e maniera del presentation es importante, incluse le uso de technicas auxiliar de character visual e auditori e le application del principio de repetition e emphase. Le habilitate pedagogic del docente pote esser cultivate. Le efficacia del instruction cresce si le discursos es consciemente adaptate al requirimentos specific del studentes. Le analyse del resultatos del examines final supporta le conclusion que studentes del tertio inferior del classe require plus repetition e emphase que studentes del tertio superior. Isto reflecte un differentia de initiativa in le acquisition de nove cognoscentias. Il es certe que le beneficio que le studente individual deriva ab instruction per discursos oral es fortemente influentiate per le factor del habituation precoce del studente mesme.

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CASE REPORTS

SYPHILITIC PAROXYSMAL COLD HEMOGLOBINURIA *

By Irvin L. Schweitzer, Major, (MC) USA, *Freeport, Illinois*

Paroxysmal cold hemoglobinuria is a rare hemolytic disorder of which there are two distinct varieties. The syphilitic form is caused by a specific hemolysin which becomes fixed to erythrocytes when the patient is chilled and causes hemolysis when the patient is subsequently warmed. It is almost invariably associated with an inactive phase of late congenital or acquired syphilis. The nonsyphilitic form is caused by a high titer of cold agglutinins and is frequently associated with vascular disorders such as the Raynaud syndrome. The following is a case of syphilitic paroxysmal cold hemoglobinuria with three aspects of special interest: (1) it occurred during an early, active phase of meningovascular syphilis; (2) a marked, transient leukopenia was demonstrated with the hemolytic episodes, and (3) intensive penicillin therapy, while improving the syphilis, had no effect on the hemolytic disorder.

Case Report

A 19 year old Negro soldier was admitted to the U. S. Army Hospital on December 8, 1954. He had been well until mid-October, 1954, when he developed a chill after standing guard on a cold night. Shortly thereafter he developed pain in both costovertebral angles and his urine became dark red in color. Within four hours his symptoms had disappeared and his urine returned to a clear yellow color. Five more such episodes occurred during the next six weeks, each following exposure to cold. During the period between paroxysms the patient was entirely asymptomatic.

There was no past history of chancre or secondary syphilis, and no known syphilis existed in other members of the patient's family. The patient had enlisted in the Army in May, 1954, at which time routine serologic tests for syphilis were negative.

Physical examination revealed a young Negro male who appeared in good health. The left pupil was slightly dilated and reacted sluggishly to light. There were no other abnormalities.

Admission laboratory studies revealed 7,500 leukocytes per cubic millimeter, with a normal differential count. There were 3,100,000 erythrocytes per cubic millimeter, the hemoglobin was 10.6 gm. per 100 c.c., and the hematocrit was 34%. A routine urinalysis was negative. The cardiolipin flocculation and cardiolipin complement fixation were positive with a quantitative titer of 1 : 32. The Donath-Landsteiner test for cold-warm hemolysins was positive on two occasions. Tests for cold agglutinins, Coombs' test for incomplete antibodies and Ham's test for acid hemolysins were negative. No sickling was seen in a sickle preparation, and the osmotic fragility of the erythrocytes was normal. The nonprotein nitrogen was 29 mg.%, the blood urea nitrogen was 13 mg.% and the total serum bilirubin was

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0.1 mg.%. Examination of the cerebrospinal fluid revealed normal pressure and dynamics. There were 332 lymphocytes per cubic millimeter, the total protein was 48 mg.% and the colloidal gold curve was 2211100000. Wassermann and cardiolipin flocculation tests were positive.

A Rosenbach test performed on December 23, 1954, is shown in figure 1. The patient's hands were immersed in ice water for 10 minutes and urine specimens were collected at hourly intervals thereafter. The first four specimens were dark red in color, the guaiac test was positive and no erythrocytes were seen on microscopic examination. The five hour specimen was clear yellow and the guaiac test was negative.

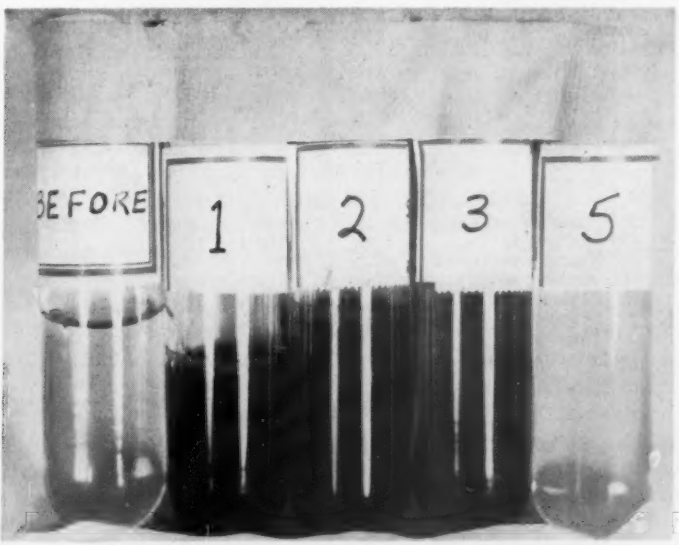

FIG. 1. Rosenbach test showing hemoglobinuria in the first three hourly urine specimens after chilling. The five hour specimen is free of hemoglobin.

Penicillin therapy was begun on December 23, 1954. A total of 18,000,000 units was given over a 30 day period. On the second day of therapy a fever of 101° F. occurred which was interpreted as a mild Herxheimer's reaction. There were no other untoward reactions to the penicillin, and the patient was asymptomatic during the remainder of his hospital course. The Rosenbach test was repeated on the tenth and thirtieth days of penicillin therapy and six weeks after it was completed. It remained positive on all occasions. Leukocyte counts performed during these tests consistently revealed a marked, transient leukopenia. This occurred mainly in the granulocytic series, with marked decrease in the percentage of neutrophils and eosinophils and a relative lymphocytosis (table 1). Direct Coombs' tests were performed before, during and after the induced hemolysis and remained negative at all times. The Donath-Landsteiner test remained positive. Reëxamination of the spinal fluid after completion of therapy revealed that the number of lymphocytes had decreased to 24 per cubic millimeter and the total protein had decreased to 29 mg.%. Because cold exposure in the form of the Rosenbach test continued to produce hemolysis six weeks after the completion of penicillin therapy, it was felt that the patient was unsuitable for duty in the chilly climate of Germany and he was evacuated to the United States.

TABLE 1

Total and Differential Leukocyte Counts During Rosenbach's Tests

Date	Leukocytes	Control Counts	Time after Chilling			
			30 Min.	1 Hour	3 Hours	5 Hours
Jan. 3, 1955	Total per cu. mm.	8,900	2,800	*	*	12,750
	Neutrophils	43%	19%	*	*	66%
	Lymphocytes	42%	77%	*	*	24%
	Monocytes	5%	2%	*	*	7%
	Eosinophils	6%	1%	*	*	2%
	Basophils	3%	1%	*	*	1%
	Stabs	1%	0	*	*	0
Jan. 27, 1955	Total per cu. mm.	10,650	3,950	9,650	11,600	11,900
	Neutrophils	49%	44%	72%	82%	82%
	Lymphocytes	35%	45%	17%	13%	11%
	Monocytes	5%	2%	1%	1%	3%
	Eosinophils	8%	1%	3%	1%	2%
	Basophils	2%	1%	0	1%	1%
	Stabs	1%	7%	7%	2%	1%
Mar. 9, 1955	Total per cu. mm.	7,100	3,850	5,600	5,080	11,050
	Neutrophils	47%	2%	51%	77%	76%
	Lymphocytes	40%	96%	48%	16%	19%
	Monocytes	1%	1%	1%	5%	3%
	Eosinophils	12%	1%	0	2%	1%
	Basophils	0	0	0	0	0
	Stabs	0	0	0	0	0

DISCUSSION

Syphilitic paroxysmal cold hemoglobinuria is a rare disease caused by a specific cold-warm hemolysin which is distinct from the nonspecific Wassermann reagin.[1, 2] This hemolysin combines with complement and becomes fixed to erythrocytes when the patient is chilled and causes hemolysis when the patient is subsequently warmed. Hemoglobinemia results and produces hemoglobinuria if the renal threshold is exceeded. Chills, fever and back pain frequently occur with the episode. Each attack may last from two to 12 hours, and the patient is usually asymptomatic between episodes.

Hemoglobinuria caused by circulating cold agglutinins clinically resembles paroxysmal cold hemoglobinuria of syphilis but may be differentiated by the following points, as listed by van Loghem:[3]

"Classic" Paroxysmal Cold Hemoglobinuria	Paroxysmal Cold Hemoglobinuria Caused by Cold Agglutinins
1. No cold agglutinins in high titer	1. Cold agglutinins in high titer present
2. Donath-Landsteiner reaction positive	2. Donath-Landsteiner test negative or nonspecific
3. Wassermann reaction positive	3. Wassermann reaction negative or incidentally positive
4. Dermolysin present	4. Dermolysin absent
5. Rashes of cold urticaria frequently observed during attack	5. No rashes of cold urticaria
6. Vascular disorders absent	6. Vascular disorders (Raynaud's syndrome) frequently present
7. Antiluetic treatment successful	7. Antiluetic treatment unsuccessful

The Donath-Landsteiner test demonstrates the presence of the cold-warm hemolysins in the patient's serum and is diagnostic of syphilitic paroxysmal cold hemoglobinuria. Guinea pig complement is added to a mixture of patient's serum and patient's erythrocytes and also to a mixture of patient's serum and control erythrocytes. Both mixtures are then chilled and warmed again. Hemolysis of both the patient's and the control erythrocytes confirms the presence of the specific cold-warm hemolysin in the patient's serum. The Rosenbach test consists of artificially inducing a hemolytic episode by immersing the patient's hands or feet in ice water. It is not specific for syphilitic cold hemoglobinuria, as it may also be positive in cold hemoglobinuria due to cold agglutinins. Some caution is required in performing this test, as excessive hemolysis may cause renal insufficiency.[4]

Paroxysmal cold hemoglobinuria is almost always associated with the late, inactive stage of congenital or acquired syphilis. Becker [5] reviewed 38 cases and found that all occurred in the late, latent seropositive stage. The case herein reported is noteworthy in that it occurred during early, active meningovascular syphilis, as evidenced by a negative serology six months prior to onset and a marked lymphocytic pleocytosis in the cerebrospinal fluid.

Intravascular hemolysis may be accompanied by a marked, transient leukopenia. The exact mechanism of this phenomenon is unknown, but Jordan and his associates [6] suggest that damaged erythrocytes cause increased erythrophagocytosis, and the leukocytes thus laden with engulfed red cells are trapped in organ capillaries. These authors studied three cases of cold hemoglobinuria and found that neutrophils, monocytes and eosinophils were all reduced about 75% after chilling. The neutrophil counts returned to normal within two hours, but the other cell counts remained low for five hours. Our tests are shown in table 1. In two tests the neutrophils were most markedly depressed. This neutropenia was accompanied by a relative lymphocytosis and returned to normal in one hour in the test in which a one-hour count was performed. In the third test (January 27, 1955) monocytic and granulocytic cells were equally depressed.

The response of paroxysmal cold hemoglobinuria to antiluetic therapy remains uncertain. The results of arsenical and heavy metal therapy were recorded in 25 cases in Becker's [5] review. Fifteen of these were reported as cured and 10 as improved. Hill [2] collected from the literature seven cases which had been treated with penicillin, and added one case of his own. Three of this series were recorded as cured, three as improved and two as unchanged. Hall [7] reported one case associated with congenital syphilis in which arsenical and penicillin had no effect. In the case herein reported, 18,000,000 units of penicillin caused a marked reduction of the pleocytosis and protein level of the cerebrospinal fluid, but the cold-induced hemolysis has persisted to date.

Summary

A case of paroxysmal cold hemoglobinuria associated with early, active meningovascular syphilis is reported. A marked, transient leukopenia was demonstrated during the cold-induced hemolytic episodes. Intensive penicillin therapy, while improving the signs of syphilis, had no apparent effect on the hemolytic disorder.

SUMMARIO IN INTERLINGUA

Cryohemoglobinuria paroxysmal syphilitic es un rar disordine hemolytic que es quasi semper associate con syphilis congenite tardive o con syphilis acquirite. Illo resulta de un specific hemolysina cryo-thermic circulante in le plasma. Iste hemolysina se attacha al erythrocytos quando le patiente es exponite a basse temperaturas e causa hemolyse quando le temperatura del ambiente del patiente es subsequentemente realtiate. Le manifestationes clinic es episodios recurrente de frigor, dorsalgia, e le production de urina rubie o nigre post exposition a basse temperaturas. Usualmente le patiente es completemente asymptomatic durante le intervallos ab un exposition a frigido usque al altere. Le test Donath-Landsteiner demonstra le specific hemolysina cryo-thermic in vitro. Iste reaction es diagnostic pro cryohemoglobinuria paroxysmal syphilitic. Le resultatos de therapia antiluetic in le correction de iste secundari disordine hemolytic non es certe. Il existe reportos de non-successo in cursos therapeutic a metallo pesante e a penicillina.

Le caso reportate in le presente articulo es de interesse special a causa del sequente rationes: (1) Illo occurreva durante un precoce phase active de syphilis meningovascular, demonstrate per un recente negativitate serologic e le presentia de marcate pleocytosis in le fluido spinal; (2) marcate grados de neutropenia transiente esseva demonstrate durante le tres episodios hemolytic inducite per le test de Rosenbach; e (3) un intense e prolongate curso therapeutic a penicillina resultava in un marcate melioration del syphilis meningovascular sed in nulle melioration del reaction hemolytic evocate per frigido.

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MEDIASTINAL EMPHYSEMA COMPLICATING MYOCARDIAL INFARCTION AND LEFT VENTRICULAR FAILURE*

By JAMES C. NASH, M.D., F.A.C.P., *Decatur, Alabama*

MEDIASTINAL emphysema, precipitated by acute failure of the left ventricle following myocardial infarction, must be considered of rare occurrence since a survey of the literature reveals only one previously reported case. In the patient

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reported by Dannish,[1] mediastinal emphysema was manifested by the sudden appearance of air in the subcutaneous tissues of the neck and supraclavicular areas, and occurred on the fourth day following acute left ventricular failure which had complicated posterior myocardial infarction. The patient eventually recovered. Dannish [1] reviewed the pathogenesis of mediastinal emphysema, emphasizing the views of Aisner and Franco [2] that precipitating or predisposing factors may be trivial or easily overlooked. Such factors may be cough, dyspnea or the forceful straining encountered in various situations and disease entities. Possible causes of mediastinal emphysema are infectious diseases, such as influenza, measles, pertussis and tuberculosis; rupture of lung abscesses or cysts; influenzal pneumonia; obstructive laryngitis; aspiration of a foreign body; pulmonary neoplasm; childbirth; positive-pressure-inhalation therapy; resuscitation by pulmotor; faulty administration of anesthesia by the closed method; lung trauma and perforation of the trachea or bronchi; rupture of the esophagus or an abdominal viscus; rarely rupture of the mediastinal septum and fenestrations of developmental origin.[3, 4] Hamman [5] drew attention to the occasional occurrence of spontaneous mediastinal emphysema.

The case herewith reported is considered of special interest because it represents not only another instance of mediastinal emphysema complicating myocardial infarction but also an addition to the known causes of death following coronary thrombosis and acute failure of the left ventricle.

Case Report

The patient, a 67 year old white female, was admitted to the Huntsville General Hospital, Huntsville, Alabama, on March 6, 1950. She had been seen at her home four weeks prior to admission in an attack of acute coronary thrombosis with posterior myocardial infarction (figure 1). At this time hospitalization was refused, and the patient subsequently proved very uncoöperative and unmanageable. She exhibited marked motor restlessness, threshing about in bed, pacing the floor, talking loudly and groaning. Episodes of hyperventilation and hysteria occurred. Approximately two weeks prior to admission to the hospital the patient was noted to be in acute left heart failure. Consequently, she was digitalized and given mercurial diuretics, with resulting improvement. However, due to lack of physical rest and coöperation in drug therapy, complete cardiac compensation was never obtained.

Upon the day of hospital admission the patient suffered a sudden severe attack of pulmonary edema, manifested by dyspnea, orthopnea, and cough productive of pinkish, frothy sputum. A few minutes later, upon my arrival at her bedside, it was noted that the tissues of her neck were rapidly swelling with air, and she began to have excruciating pain in her anterior chest. Immediate hospital admission was obtained. Initial examination revealed a severe state of shock and peripheral vascular collapse. The subcutaneous emphysema had rapidly progressed to involve the tissues of the neck, face and upper chest to a tremendous extent. The patient was gasping for breath and was very cyanotic. Moist râles, wheezes and rhonchi were noted over both sides of the chest. A crunching sound, synchronous with the heart beat, was heard over the entire precordium. There were no definite physical signs of a pneumothorax. Laryngeal stridor was not noted, and it was felt that tracheal obstruction of a significant degree did not exist. A portable bedside x-ray of the chest confirmed the presence of mediastinal emphysema (figure 2).

Within a few minutes of admission to the hospital, multiple small incisions into the subcutaneous tissue of the supraclavicular and suprasternal areas were made, and

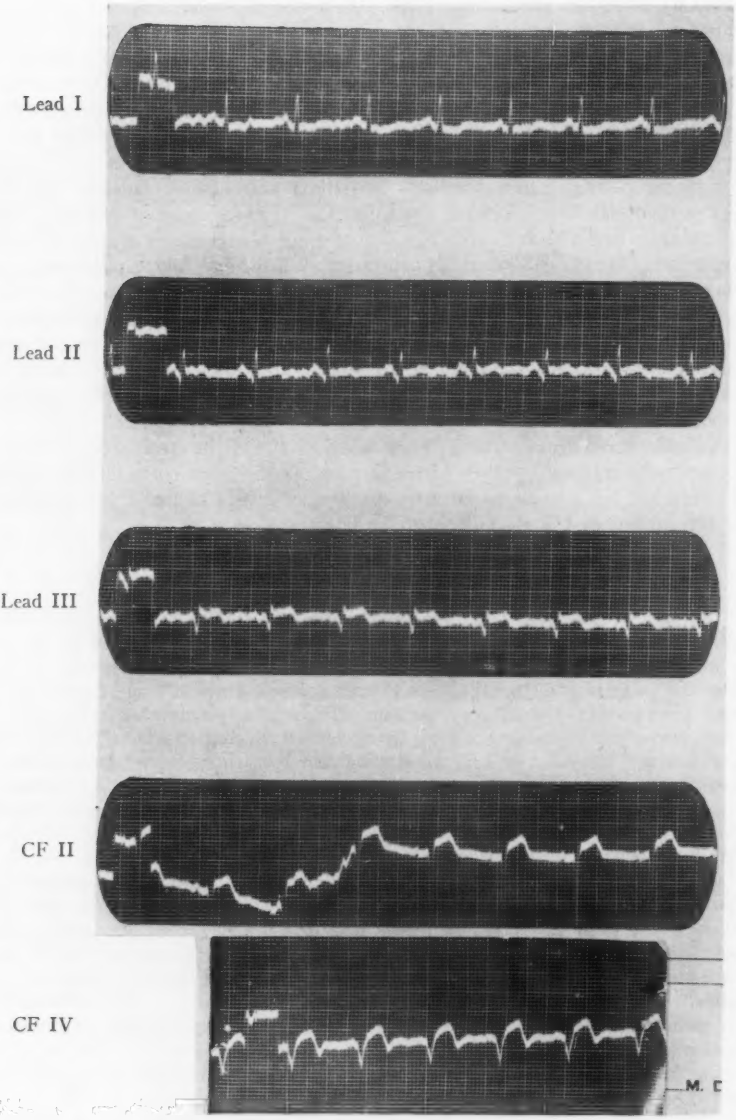

FIG. 1. Electrocardiogram showing acute myocardial infarction.

a needle was inserted in the third intercostal space just to the left of the sternum. From this point a considerable amount of air was aspirated. There was no relief of symptoms, and the accumulation of air continued at a rapid rate. Oxygen and stimulants were administered to combat the shock and anoxia. All these measures

were to no avail, and the patient died approximately one hour after admission. Permission for autopsy could not be secured.

Discussion

The etiologic factors leading to pulmonic interstitial emphysema, the precursor of mediastinal emphysema, are of particular importance because they help to explain many obscure phenomena associated with this condition. The Macklins [6, 7] have done much to clarify the pathogenesis of these conditions. According to their concept, sudden and pronounced pressure changes (pressure gradients) between the intra-alveolar air and pulmonary intravascular blood take place

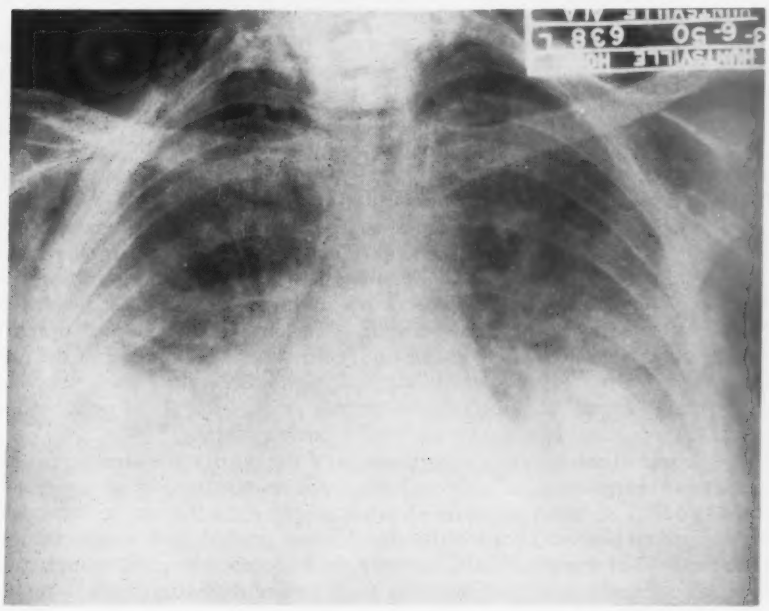

Fig. 2. Bedside chest x-ray showing massive pulmonary edema and emphysema of the subcutaneous tissues and mediastinum.

to produce extravasation of air (pulmonic interstitial emphysema) into the perivascular sheaths and thence into the tissues of the mediastinum. Such a pressure gradient may be produced by localized overdistention of lung tissue without corresponding widening of the lumen of blood vessels which the overdistended alveoli border. As a consequence of the pressure gradient, the alveoli rupture. If the alveoli are "marginal," that is, have their bases resting against other structures such as bronchi, bronchioles, blood vessels, connective tissue or pleura, then the dissection of air released must take place in the underlying connective tissue, chiefly along the sheaths of blood vessels. Cough, dyspnea, forceful straining and other procedures involving the Valsalva maneuver may produce such local-

ized overinflation of lung tissue, and no doubt were instrumental in the case reported above.

According to the Macklins,[6, 7] a pressure gradient may also be produced as a result of reduction of the caliber of blood vessels brought about through a decrease in blood flow (1) by a lessened return of venous blood to the right side of the heart; (2) by a failing heart which cannot pump the normal amount of blood to the lungs; (3) by pulmonary arterial obstruction, as in pulmonary embolism; and (4) by pulmonary stenosis or insufficiency. Since the patient described was in a state of acute heart failure and pulmonary edema, and presented severe racking cough, acute dyspnea and marked motor restlessness, it would seem likely that both localized overinflation of the lung and decrease in blood flow in the pulmonary vessels accounted for the development of mediastinal emphysema through the various mechanisms described above.

The diagnosis of mediastinal emphysema in the case presented was apparent both by the sudden appearance of air in the subcutaneous tissues of the neck, supraclavicular and suprasternal areas, and the auscultatory evidence over the precordium of crunching sounds, synchronous with the heart beat (mediastinal crepitation or Hamman's sign).[4] Confirmation was obtained by the bedside chest roentgenogram, which revealed linear areas of translucency bordering the mediastinum, representing air beneath the mediastinal pleura.

The diagnosis of mediastinal emphysema in patients with widespread subcutaneous emphysema may be difficult. The mediastinum may appear free from air at the time of x-ray examination or may be obscured by the overlying subcutaneous emphysema. In this connection, a lateral view of the chest is valuable, air being often visible behind the sternum. The presence of marked dyspnea, cyanosis and dilated neck veins in cases of subcutaneous emphysema of the neck and supraclavicular areas is of great diagnostic significance, since these symptoms and signs are generally lacking in subcutaneous emphysema of the neck without coexisting mediastinal emphysema or tension pneumothorax.[4, 8]

The degree of interference with functions of the mediastinal structures—and therefore the variation of clinical features, such as retrosternal pain, dyspnea, cyanosis and fall in blood pressure—depends chiefly upon the rate of increase in intramediastinal pressure, particularly the pressure exerted upon easily compressible veins.[9] The speed with which excess air is absorbed into subcutaneous tissues is also important, since pressure effects on the mediastinal structures are thereby lessened. A relatively small amount of air trapped in a closed space within the mediastinum may prove rapidly fatal. Ballon and Francis[10] found experimentally that when mediastinal emphysema is marked, subcutaneous emphysema is usually slight, and vice versa.

Besides these effects upon circulation, a certain amount of respiratory impediment occurs due to the splinting action of air on the interstitial tissues of the lung and mediastinum (Macklin's air block). Master, Kalter and Dach[11] noted that angina pectoris, coronary thrombosis, pericarditis, pulmonary infarction and pneumonia may be simulated.

The treatment afforded the patient presented consisted of oxygen and stimulants to combat the anoxia and shock; opiates to relieve the excruciating pain; multiple small incisions into the subcutaneous tissues of the supraclavicular and suprasternal areas to permit more rapid egress of air from the mediastinum; and

needle aspiration of air from a point in the third intercostal space just to the left of the sternum in an effort to decompress the mediastinum. Other recommended procedures of treatment, not used in this case, are tracheotomy and cervical or thoracic mediastinotomy. Lindskog and Liebow,[8] in discussing the value of tracheotomy, state that the procedure decompresses the mediastinum, thus indirectly taking pressure off the trachea, bronchi and great veins; furnishes an adequate airway and removes the possibility of building up further pressure by cough, hyperpnea and straining, since the glottis is bypassed. Hochberg [9] advocates cervical or thoracic mediastinotomy and, in addition, deflation of the pleural cavity via water trap where tension pneumothorax coexists.

Summary

A case is reported of another instance of mediastinal emphysema complicating myocardial infarction and left ventricular failure. Death resulted. The pathogenesis, etiology, diagnosis and treatment of mediastinal emphysema are discussed.

Summario in Interlingua

Emphysema mediastinal, precipitate per acute disfallimento del ventriculo sinistre post infarcimento myocardial, debe esser considerate como un occurrentia rar, proque un revista del litteratura revela solmente un caso precedente illo de iste reporto. In le pathogenese de emphysema mediastinal, le possibile factores predisponente o pricipitante include tusse, dyspnea, o excesso de stress e effortio effectuate per varie situationes e conditiones pathologic.

In le presente caso il se tracta de un feminina blanc de 67 annos de etate qui disveloppava, quatro septimanas ante su morte, acute thrombosis coronari e infarcimento postero-myocardial. Occurreva un psychosis del typo maniaco-depressive, e hospitalisation esseva refusate. Duo septimanas post le attacco initial, le patiente disveloppava acute disfallimento sinistro-cardiac. Le tractamento consisteva de digitalisation e le uso de diureticos. Complete compensation cardiac non esseva effectuate. Le die de su morte, le patiente disveloppava subitanee edema pulmonar de forma acute e sever, sequite per emphysema subcutanee de progresso rapide que primo afficeva le tessutos del collo e postea invadeva le facie e le pariete superothoracic. Alte grados de dyspnea, cyanosis, e dolores thoracic esseva aspectos associate, e le patiente collabeva. Un sono crepitante, synchrone con le pulso cardiac, esseva audibile supra le integre precordio (signo de Hamman). Le roentgenogramma thoracic obtenite per apparato mobile confirmava le presentia de emphysema mediastinal. Multiple parve incisiones in le afficite tessutos subcutanee, aspiration per agulia de grande quantitates de aere ab le tertie interspatio sinistro-anterior, le administration de oxygeno, e varie stimulantes remaneva sin effecto. Le patiente moriva un hora post su transferimento al hospital. Le permission de executar un necropsia non poteva esser obtenite.

In su discussion de factores etiologic e del pathogenese, le autor sublinea le theoria del gradiente de pression de Macklins. Subite gradientes inter le aere intraalveolar e le sanguine intravascular pulmonic que produce emphysema interstitial pulmonic e subsequentemente emphysema mediastinal pote resultar ab le localisate hyperinflation del tessutos pulmonar e un reduction del fluxo sanguinee in le vasos pulmonar.

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ALVEOLAR CELL TUMOR: REPORT OF A CASE AND EVALUATION OF DIAGNOSTIC PROCEDURES *

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ALVEOLAR cell tumor (pulmonary adenomatosis, bronchiolar carcinoma) is a condition which must be considered in the differential diagnosis of both discrete and diffuse pulmonary lesions. We believe the following case to be of interest because a chest x-ray was reported as normal a relatively short time before the abnormal film was taken, and the progression of the disease was well demonstrated by serial x-ray examinations over a period of approximately 18 months.

Our own experience has led us to the conclusion that a brief evaluation of diagnostic methods would be useful. Theories regarding the origin of the particular tissue have been thoroughly discussed in other articles,[1-15] and various authors have reviewed at intervals the cases available to them at that time. We do not intend in a short paper to discuss the relation of alveolar cell tumor to the disease of sheep known as jagziekte.

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The opinions expressed in this article are not necessarily those of the Department of the Navy or the Department of Defense.

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Case Report

The patient, a 41 year old nurse, was admitted to the hospital in March, 1952, during the fifth month of her first pregnancy. She had been in good health, but for five weeks had been aware of a pulling pain under the left breast which seemed to occur with coughing, deep breathing or any type of exertion. For three weeks she had been aware of moderate shortness of breath on exertion. There had been no respiratory tract infection since the previous winter, and there had been a rare, non-productive cough. There had been a weight gain of six pounds during pregnancy

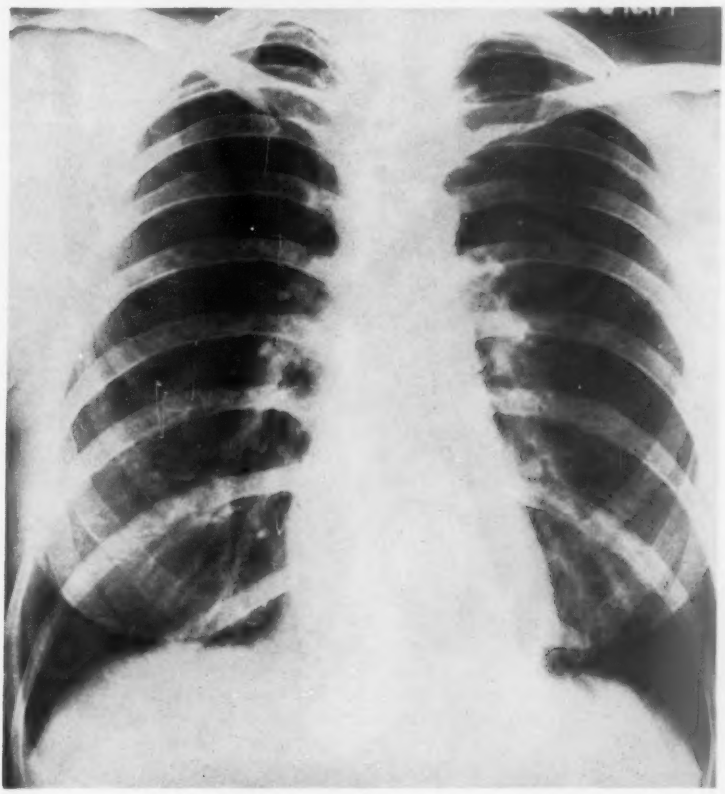

Fig. 1. X-ray of chest on routine examination two years prior to present illness.

and no fluctuation in a normal blood pressure. She had noticed slight swelling of her ankles during pregnancy. For the previous two years she had lived in the Chesapeake Bay area, except for two short visits to Louisiana and one to Rhode Island.

Routine chest x-rays taken two years before (figure 1) and two months before admission were normal. A film taken two weeks before admission showed multiple small areas of increased density, particularly in the mid-lung fields, which were not very prominent and were thought to be of minimal clinical significance, probably

related to increased vascularity of pregnancy. The last x-ray was a routine procedure incident to separation from the Service. However, it was because of this finding that she was hospitalized.

A review of symptoms by systems was negative. As a child she had had measles, whooping cough, mumps and chicken pox. In 1931 she twice had had laryngitis, then had had a tonsillectomy. In 1934 the appendix and the right ovary were removed. In 1941 she had an operation for halux valgus, and in 1946 she had diphtheria followed by anemia. There had been no injuries.

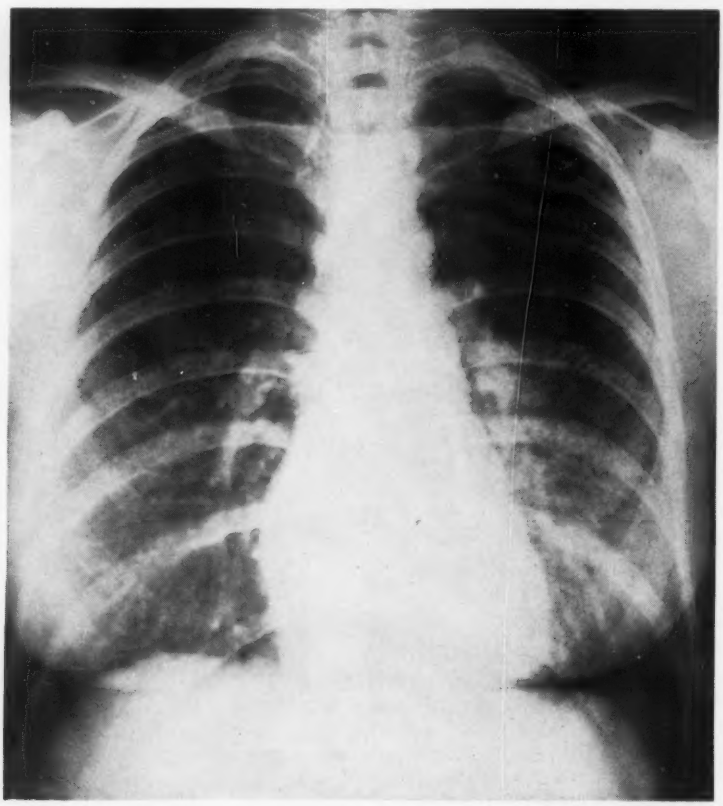

FIG. 2. Chest x-ray on admission.

There was no history of familial diseases; however, her husband had been under observation for an apical pulmonary lesion which was probably quiescent tuberculosis.

Physical examination showed a well developed, well nourished white female who did not appear acutely or chronically ill. Her hair was rather grayer than average for her age. The head, neck, thyroid, ears, nose, throat and eyes, including fundi, were normal. The chest was symmetric and the chest expansion was normal and bilaterally equal. The breasts were normal except for the expected changes of pregnancy. The lungs were clear to percussion and auscultation. The heart was

not enlarged, no murmurs were heard, and the rhythm was regular. The abdomen was negative except for a uterus enlarged to just below the umbilicus. There was no lymphadenopathy. The extremities were negative, and the neurologic examination was negative. The pelvic organs had been found to be normal by the obstetricians.

The initial laboratory studies showed a white blood count of 9,000, with a normal differential, a hemoglobin of 12.5 gm., a sedimentation rate of 13 mm. in one hour (Cutler), a normal urinalysis and a negative blood Kahn.

X-ray of the chest in the postero-anterior and right lateral positions showed a prominent vascular pattern throughout both lung fields, with multiple small, soft tissue densities which were believed to represent vascular shadows viewed axially (figure 2).

The electrocardiogram was normal. Tuberculin tests in the first and second dilutions were negative. The vital capacity was 2.8 L., or 86% of normal for her height. She was afebrile. The pulse and respiratory rates remained normal. The blood pressure varied from 96/62 to 114/68 mm. of Hg.

The pain under the left breast recurred at intervals but was not constant. The vital capacity remained about the same during the remainder of the pregnancy. The blood count and the sedimentation rate remained normal. There was a progressive increase in the nodularity noted by chest x-ray. It was most prominent in the mid-portion of the lungs and spared the extreme costophrenic angles. Late in pregnancy the lesions began to be confluent (figure 3). In view of the asymptomatic state of the patient, the clinicians and the radiologists considered as possibilities: metastatic malignancy, sarcoidosis and pulmonary adenomatosis. At no time was there any sputum and rarely was there a cough.

On July 9, 1952, she delivered a living male infant after a normal and uneventful labor of five hours. The placenta was intact and grossly normal.

Starting four weeks after delivery, intensive studies were carried out which are summarized as follows: Repeat tuberculin tests were negative in both dilutions, as were histoplasmin and coccidioidin skin tests. Various examiners were unable to palpate any abnormalities of the thyroid, breasts, lymph nodes or abdominal organs. Repeat urinalyses, including Bence Jones protein, were normal. Serum proteins were: albumin, 3.73 gm.; globulin, 2.28 gm. Serum calcium was 10.73 mg.; phosphorus, 4.75 mg. A series of three gastric washings was cultured and later was reported negative.

X-rays of the hands, upper gastrointestinal tract, small bowel and colon were normal. Excretory urograms were normal.

An ophthalmologist was unable to find any disease of the uveal tract, iris or fundus. On bronchoscopy no abnormalities were noted except that, on touching the bronchial mucosa, petechiae appeared; however, there was no gross bleeding. The bronchial washings were negative for malignant cells, and no fungi or acid-fast bacilli could be cultured. Clot retraction, red cell fragility, bleeding and clotting times were normal. A muscle biopsy was normal, as was the bone marrow. No fungi could be grown on bone marrow culture. Cystoscopy and retrograde pyelography were normal.

During the patient's postpartum period she returned to her usual weight of 130 pounds. The chest pain became more marked after delivery and would appear on bending, twisting or lying on the left side. No skin lesions were seen at any time. She remained afebrile, and the vital capacity remained unchanged, having been as high as 3.2 L. during late pregnancy. There was no change in the leukocyte or erythrocyte counts. Shortness of breath became slowly but progressively more marked. Following delivery there was a decline in the vital capacity.

Because the above procedures had failed to establish the etiology of the pulmonary lesion, on November 24, 1952, a thoracotomy, left chest, and lung biopsy

were done. The entire lung had a marked nodular appearance, as did the parietal pleura and the pericardium. Approximately 300 c.c. of rather cloudy serous fluid were found. A piece of lung tissue was taken for further examination. The pathologist reported that grossly there were small umbilicated foci of moderately firm gray tissue measuring 2 to 3 mm. in diameter. Some of these were confluent. Microscopic examination (figure 4) showed the pleural surfaces mildly thickened by connective tissue and more vascular than usual. Some of the alveoli had a normal appearance, but for the most part they were lined with cells characterized by the

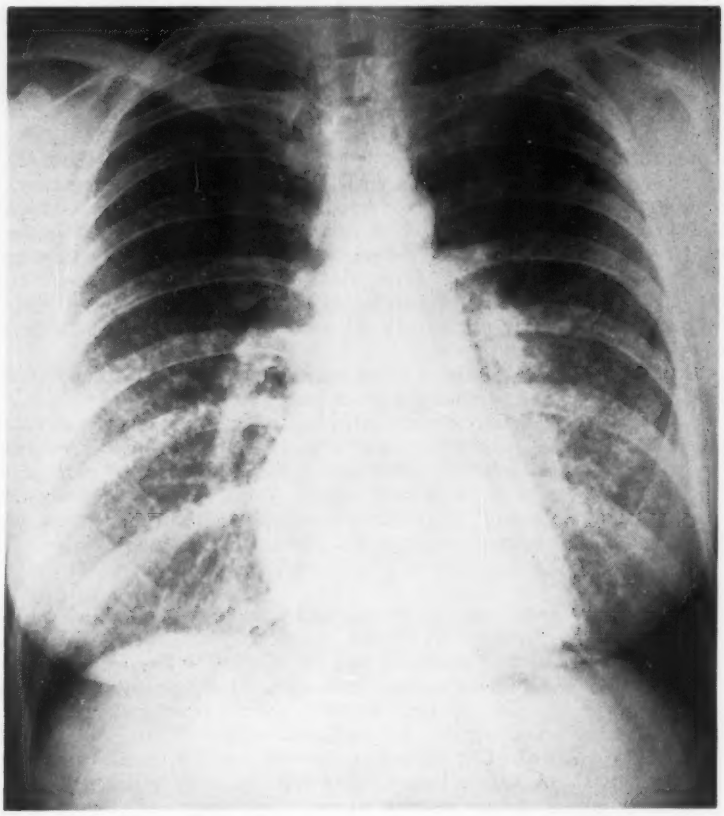

FIG. 3. Chest x-ray late in the course of the disease.

following: The cells were, as a rule, tall columnar, and somewhat bronchial, epithelium. The cytoplasm was abundant and faintly eosinophilic in staining reaction. Small granules were frequently noted, and nuclei were quite large. There were frequent irregularities in the nuclear membranes. Hyperchromism was prominent in some areas. Mitotic figures were not seen often and, when seen, were found in the more atypical nuclei. An occasional cell had a vacuolated cytoplasm. Sometimes the cells occurred in a single layer, but at times they were multilayered and not infrequently were found in solid masses which were separated into small lobules by deli-

cate connective tissue septa. The involvement of pulmonary parenchyma was extensive but had a patchy distribution. The bronchioles were difficult to distinguish, but in those seen no normal appearing epithelium was seen. They were all lined by cells of the type described above. The lesions were thought to represent a primary tumor of the lung, rather than metastases. They were histologically similar to those lesions described as alveolar cell carcinoma of the lung or bronchiolar carcinoma.

There were no remarkable postoperative reactions, but her course clinically was progressively downhill, with weight loss, muscle wasting due to being in bed, and increasing chest pain and dyspnea. Cortisone by mouth was started and maintained at a dose of 100 mg. a day. Later, small doses of x-ray therapy were given over various chest portals. X-ray examinations of the chest at intervals showed a constant picture after the postoperative accumulation of fluid cleared (figure 5).

On July 3, 1953, the patient developed clonic tremors of the left leg which at first were intermittent and then became continuous. That evening she became

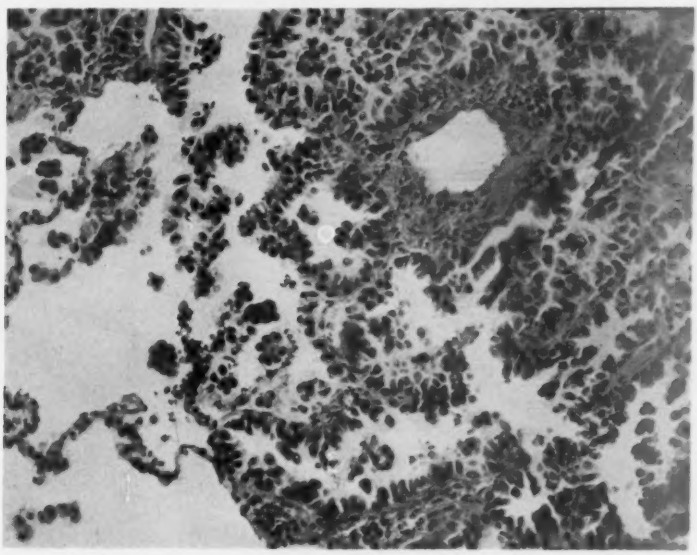

FIG. 4. Microscopic section of the lung from biopsy specimen.

extremely apprehensive, perspired profusely, and was found to have a pulse rate of 160 and a blood pressure of 130/90 mm. of Hg. An electrocardiogram showed a supraventricular tachycardia. The tachycardia failed to respond to various modes of treatment, cyanosis became more marked, breathing more labored, and the patient died early on July 4, 1953, with the heart action continuing for about 15 minutes after respiration ceased.

The gross findings at autopsy were those of a well developed, well nourished 42 year old white female measuring 66 inches and estimated to weigh 110 pounds. There was no jaundice, edema or cyanosis. When the pleural cavity was opened a few fibrous interpleural adhesions were present posteriorly on the right. The left pleural space was obliterated by dense fibrous adhesions. The lungs combined weighed 1,400 gm. The lung parenchyma was studded throughout with 2 to 3 mm. gray nodules which, when sectioned, appeared umbilicated. Except for a small area

in the anterior portion of the right lower lobe, no aeration could be detected. The hilar lymph nodes were hypertrophied. The heart weighed 310 gm. A few epicardial petechial hemorrhages were noted. There was mild atherosclerosis about the coronary ostia.

The abdominal organs were not remarkable except for slight fibrosis of the parenchyma of the spleen, mild hypertrophy of the gastric wall in the region of the pylorus, and a pancreas slightly more brown than normal. The adrenals weighed 4 gm. each and, on sectioning, both cortex and medulla were thinned. The right fallopian tube and ovary were surgically absent. No lymph node hypertrophy was

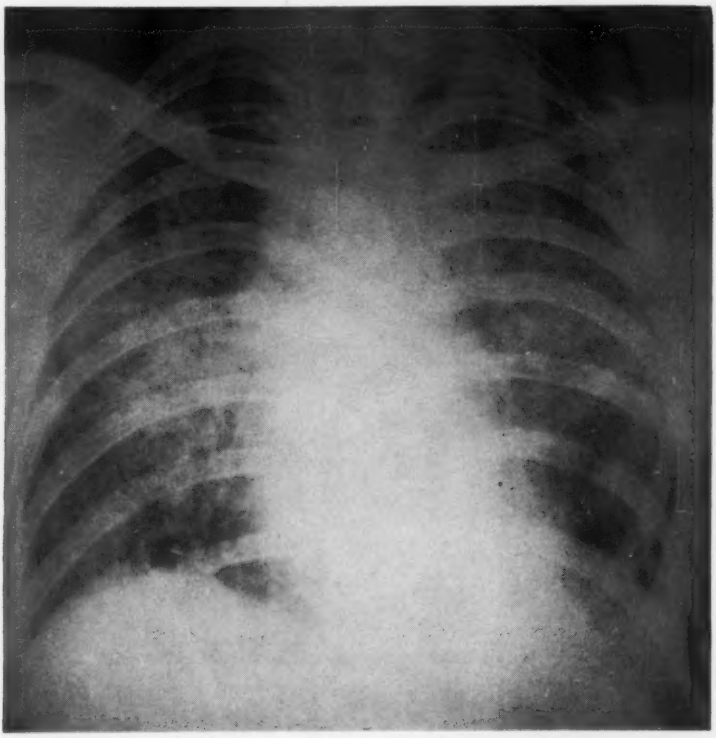

FIG. 5. Chest x-ray following thoracotomy for biopsy.

encountered. The neck organs were entirely normal. Grossly the brain appeared normal and weighed 1,250 gm.

Microscopically the heart showed a mild subendocardial infiltration of polys and lymphocytes. The same feature was noted in the adjacent superficial myocardium. Multiple sections of the lungs from all lobes had a similar histology. There were patchy foci of neoplastic tissue in which the general architecture of lung was preserved. Terminal bronchioles and alveoli were lined by columnar-type cells with hyperchromatic nuclei and eosinophilic cytoplasm. Most of the cells were uniform, but occasional mitoses were seen. Many alveoli had tiny papillations projecting into their lumens, while many more were filled with exfoliated cells like

those described above. A few alveolar spaces were filled with some sheets of neoplastic cells. In some areas the neoplastic foci were confluent. Some were seen as excrescences fanning out from bronchioles. It was difficult to ascertain the point in the bronchiole where the epithelial lining became neoplastic, so closely did it mimic the normal. In most instances it was difficult to visualize cilia, but some of the neoplastic cells were definitely ciliated. Lung parenchyma away from neoplastic foci showed engorgement of small vessels and alveolar capillaries. Many alveoli were filled with an eosin-staining homogeneous substance. Focally there was diffuse infiltration of polys and macrophages. These latter were also seen about the less dense tumor foci. Some alveoli were filled with discrete red blood cells. Sections taken from the left lung revealed a thickened fibrotic pleura and, in the operative area, neoplastic nests were seen in dense connective tissue. One focus was seen in a blood vessel (figure 6).

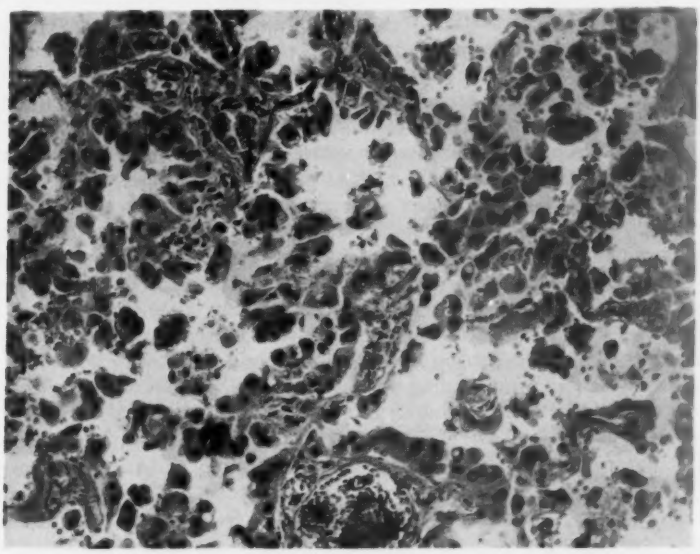

FIG. 6. Microscopic section of the lung at autopsy.

In the liver the central veins were engorged and adjacent sinusoids dilated and frequently filled with red blood cells. The splenic follicles were decreased in number, and engorgement of the pulp was the most prominent feature. Associated were macrophages filled with yellow-brown pigment. In the pancreas there was an increase in size and number of islets. In the adrenals, although grossly atrophic, normal architecture prevailed. In the kidneys, engorgement of capillaries and glomerular tufts was prominent. An occasional hyaline cast was seen in collecting tubules. The uterus, ovary and breasts were normal. Multiple sections of the brain, including cortex, midbrain, medulla and cerebellum, were examined. Pituitary colloid was diffusely scattered throughout the anterior lobe. In the capsule and along the stalk were small nests of neoplasm similar to that seen in the lungs. In the arachnoid of several sections were small neoplastic nests identical to those in the pituitary sections. One section through the lenticular nucleus revealed focal metastatic carcinoma. Nests were arranged on connective tissue stalks with delicate vas-

cularized stroma. Some created papillary formations. Most were single layered and columnar, with some cells appearing to be ciliated.

This patient had been radiologically and physically normal at the time of her examination two months prior to admission. Within six weeks of the time of first examination, equivocal x-ray changes were apparent in both lung fields. Symptoms had appeared which, because of progress of pregnancy and mildness, were not considered even in retrospect to be specific for pulmonary disease, with the possible exception of the chest pain. The disease in this case was bilateral at all times, and we concur with the opinion of the majority of authors that this disease is usually multicentric.[1, 4, 6, 10, 11, 16]

There was nothing specific in any of the chest x-rays which would lead to a diagnosis of alveolar cell tumor. This accords with the observations of others.

Bronchoscopic visualization was not helpful, as has been reported by others,[8, 10, 17] and unfortunately the bronchial washings were negative for tumor cells. If this last procedure had been positive, it would have saved the patient the additional discomfort of her course following the thoracotomy. The lack of sputum interdicted one source of material for cytologic examination.

In an evaluation of diagnostic procedures in conditions involving the chest the roentgenologic study is of the highest priority. However, in this particular condition chest x-ray has not been of much diagnostic help, as the pattern in the lungs may resemble lobar pneumonia, bronchopneumonia, tuberculosis, bronchogenic carcinoma, sarcoidosis, fungus infections, bronchiectasis and pneumoconiosis.[18, 19, 20] While the usual distribution of alveolar cell tumor follows either a nodular or a diffuse pattern, a small percentage may show pleural effusion [14, 15] or cavitation.[10, 15] Ordinarily it is a progressive pattern, but at times the disease apparently remains localized in one lobe for a period of years.[6, 16, 18] Not infrequently the earliest x-ray finding will be a solitary, circumscribed peripheral lesion in the lung.[8, 15] The value of bronchography is equivocal, having been reported useless [20] as well as helpful.[21]

Laboratory procedures in the spheres of hematology and chemistry have never contributed except in a negative way to the diagnosis. Recognition of this disease depends on microscopic examination of tissue. The abnormal cells may be found with varying degrees of frequency in three locations: lung, lymph nodes and sputum. Open thoracotomy and recovery of an adequate bit of lung tissue would seem to be the most accurate means of diagnosis; however, the small but definite risk of anesthesia and operation, plus the postoperative discomfort, weighs heavily against this as the method of first choice. The simplest procedure is cytologic study of sputum and bronchial washings. There will be a respectable percentage of false-negative reports, as well as a certain number of patients who have no sputum. Nevertheless, this would seem to be an approach which should be followed exhaustively before one progresses to more traumatic procedures.[4, 8, 10, 12, 15, 17, 22, 23, 24]

If cytologic examination of bronchial secretions has proved fruitless, the next step might well be study of a retroclavian lymph node by a procedure which has been well defined.[25, 26, 27] The presence of the typical tumor cells in the accessible lymph nodes could be a deciding factor in a consideration of operability or inoperability of the pulmonary lesion. The regional lymph nodes have been reported to be not involved by a few authors,[18, 28, 29] while a larger number report

characteristic tumor cells in the regional nodes.[1, 6, 10, 12, 13, 14, 15, 22] It would be highly desirable, in future case reports, to give a more exact location of the positive and negative intrathoracic and suprathoracic nodes, as this would furnish a basis for estimating probabilities when resection was being considered.

In considering the choice between thoracotomy and needle aspiration biopsy, one must weigh the morbidity of each procedure against the probable yield. This decision will be modified by the location of the lesion in the chest by x-ray and by the experience of the surgeon.

If an individual presents a well localized lesion by x-ray, and examination of sputum and bronchoscopy is negative, then thoracotomy and excision of the lesion without further diagnostic procedures and delay would currently seem to be the proper course.

At no time did this case seem to be a good candidate for resection, because the process appeared to be bilateral from the start; however, resection would seem to be the procedure of choice in cases where, by x-ray, the disease appears to be localized to one lobe.[7, 8, 10, 12, 15, 16, 17, 23] External radiation therapy is only slightly palliative, if effective at all,[6, 8, 20, 23, 24] while drugs such as Teropterin and nitrogen mustard are reported to be ineffective.[8] In this case, cortisone had no effect that could be evaluated objectively, although psychologically it may have been of some value.

Summary

A case is presented of apparently multicentric alveolar cell tumor, with discovery of the bilateral process six weeks after a normal chest x-ray. Diagnostic procedures are evaluated and therapy is discussed briefly.

Summario in Interlingua

Le caso hic presentate es interessante a causa del normal roentgenogrammas thoracic reportate a un periodo relativemente breve ante le discoperta original del morbo.

Un infirmera de 41 annos de etate esseva admittite al hospital durante le quinte mense de su prime pregnantia a causa de un sensation tirante intra le thorace sinistre post tusse o inspiration profunde e a causa de un roentgenogramma suspecte. Roentgenogrammas thoracic obtenite routinarimente duo annos e de novo duo menses ante le admission habeva essite normal. Un pellicula prendite duo septimanas ante le admission monstrava multiple parve areas de densitate augmentate in ambe pulmones. Iste areas non esseva multo prominente. Le complete examine physic e omne studios laboratorial esseva negative. Le patiente produceva nulle sputo.

Le parturition occurreva a termino e esseva normal. Durante e post le pregnantia, le densitates in le roentgenogramma thoracic se augmentava progressivemente. Extense studios additional interprendite post le fin del pregnantia esseva omnes normal. Le sol anormalitate apparente esseva le reducite capacitate vital. Bronchoscopia e le studio cytologic de lavages bronchial remaneva negative. Biopsia pulmonar per thoracotomia esseva effectuate circa septe menses post le declaration del dolores thoracic e le prime questionabile roentgenogramma thoracic. Le examine microscopic del specimen bioptic revelava carcinoma de cellulas alveolar. Le patiente moriva 15 menses post le apparition del dolores thoracic. Le necropsia revelava un affection diffuse de ambe pulmones, con nodulos de tessuto tumoral de 2 a 3 mm de diametro e con metastases al cerebro. Roentgenotherapia e therapia a steroides habeva remanite inefficace.

Un revista del litteratura indica que le diagnose depende del recognition de cellulas tumorose in specimens del pulmon, de sputo, o de nodos lymphatic. Le prime passo a prender es le exacte studio de lavages bronchial; le secunde, biopsia de un nodo lymphatic retroclavicular; le tertie, biopsia per thoracotomia aperte.

Es recommendate que le pathologos reporta in le futuro plus exactemente le sito de tumorifere nodos lymphatic in le thorace, si tales es incontrate. Iste information permitte predicer le probabilitate de successo in le diagnose per biopsia de nodos lymphatic retroclavicular.

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THE NEPHROTOXIC LESION OF ETHYLENE GLYCOL *

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Needle biopsy of the kidney affords a unique opportunity to study the pathology of renal disease in the living patient.[1] This relatively new and valuable investigative tool was employed in one of two recently observed nonfatal cases of acute renal insufficiency due to ethylene glycol. The demonstration of oxalate crystals in the renal tubules represents the first reported premortem confirmation of a finding well established in autopsy material.[2] Observations on additional histologic changes and clinical course manifested by these patients may be of sufficient interest to warrant a description and brief review of ethylene glycol toxicity.

Ethylene glycol was first prepared 100 years ago but attracted little attention from clinicians until the 1920's, when the shortage of glycerine induced by World War I stimulated a widespread search by the pharmaceutical industry for nontoxic substitutes. Among the compounds tested were the polyhydric alcohols or glycols. These studies established rather marked differences in toxicity, sites of damage, and histologic alterations produced by the various glycols.[3, 4]

Ethylene glycol, a colorless, odorless liquid with a structural formula of $(CH_2)_2(OH)_2$, was reported to be fatal to a variety of laboratory animals when administered in drinking water, with death usually due to cardiac failure, pulmonary edema or acute renal insufficiency. The rapid conversion of ethylene glycol to oxalic acid, first noted by Pohl in 1895,[5] was confirmed, and estimates of the fraction recoverable in the urine as oxalic acid ranged from 3 to 10%.[5, 6]

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The kidneys of animals poisoned with either compound regularly showed deposition of calcium oxalate crystals in tubular lumina and varying degrees of epithelial cell degeneration, depending on the length of the survival period.

In the following years the development of new industrial uses for ethylene glycol, e.g., in the manufacture of antifreeze solutions, produced a demand greater than that for all the other glycols combined. In the United States alone the production rose from a negligible amount in 1937 to 341,000 tons in 1951.[7] This increased availability was reflected in a number of reports, beginning in 1930,[8] describing human fatalities following the ingestion of antifreeze. Such reports[2, 5, 9] demonstrate a remarkable constancy of clinical and pathologic pictures which are summarized in the following paragraphs. It is evident that the nature of the syndrome usually precludes detailed observations of the renal effects, and descriptions of renal histology in surviving patients are nonexistent.

Clinical Picture

Ethylene glycol has been described as having a bittersweet taste. The present authors report (on the basis of cautious sipping) a decidedly unpleasant, waxy taste when reagent-grade ethylene glycol is tested. Its combination with water is exothermic, imparting an immediate feeling of warmth to the tongue and pharynx. Fatal doses are apparently quite variable, since death has been reported from the ingestion of 100 ml., while other patients have survived 240 ml.[6]

Events following ingestion may be conveniently, if arbitrarily, divided into three stages, with death usually occurring in one of the first two:

1. *Central Nervous System Effects:* The first signs of ethylene glycol poisoning are manifested within from 30 minutes to 12 hours, or occasionally longer. The smaller doses produce intoxication closely resembling that due to ethanol. In the absence of a history, the diagnosis is suggested by the picture of acute alcoholism without a characteristic breath odor. With larger doses the picture is one of stupor, coma, convulsions and death. On occasion, patients may progress rapidly into shock and die within 24 hours. Nausea, vomiting and hematemesis are sometimes prominent, and the urine usually contains protein and oxalate crystals.

The corresponding microscopic pathology in the brain includes parenchymal edema, capillary engorgement and hemorrhage, and Betz's cell and Purkinje's cell chromatolysis, with perivascular and meningeal deposition of calcium oxalate crystals. The kidneys at this stage show only crystal deposition in tubular lumina.

2. *Cardiopulmonary Effects:* With survival beyond the first 12 to 24 hours, the patient may exhibit rapidly progressive tachypnea, cyanosis, pulmonary edema and, frequently, death. Clearcut evidence of cardiac failure is not necessarily present, and it is possible that the pulmonary edema may be of central nervous system origin.

On section, the lungs show extensive edema, early bronchopneumonia and, very rarely, calcium oxalate crystal deposition. Cardiac pathology includes petechial hemorrhage and myocardial dilatation.

3. *Renal Effects:* Survival beyond the second or third day, a rare event in the fatal cases, usually permits the recognition of some degree of renal impairment. Flank pain and tenderness over the kidneys is especially frequent, and functional impairment varies from proteinuria to anuria and death in uremia. Boemke [10] described a patient who died after 10 days of anuria following ethylene glycol ingestion. The kidneys showed calcium oxalate crystals and fat droplets in the tubular epithelial cells. Kahn [9] reported a surviving case in whom retention of nitrogen occurred along with proteinuria, but urine outputs were not stated.

The microscopic pathology in the majority of the reported cases consists of oxalate crystal deposition with either normal epithelial architecture or slight degeneration, depending on the interval from ingestion to death. An important exception to this is provided by Widman's two patients, who died after several days of anuria. Here, the kidneys showed extensive epithelial destruction as well as calcium oxalate crystallization.[11]

The following two cases illustrate some of the above points and afford an opportunity for discussion of the renal lesion in ethylene glycol poisoning.

Case Reports

Case 1. A 17 year old white male prison inmate drank 70 to 90 ml. of "Zerex" on the afternoon of August 6, 1955. "Zerex" is an antifreeze containing 95% ethylene glycol, the remainder consisting of water, octyl alcohol and trace amounts of antirust compounds. He noted a sweet taste and within 20 minutes felt moderately numb. Transient blurring of vision occurred, but he was able to attend a movie that evening and go back to his room unaided. He awoke the next morning with violent retching and hematemesis which persisted and led to his hospitalization at 3:00 p.m. on August 7, 1955. His appearance on the first hospital day was described as hyperpneic and lethargic. Blood pressure was 120/50 mm. of Hg. There were headache, frequent profuse vomiting and right flank pain radiating to the testis. Twenty-four hour urine output was 100 ml. The patient improved over the next few days, but urine output remained below 250 ml. per day with intakes of 700 to 1,000 ml. Accordingly, on the fifth hospital day he was transferred to Georgetown University Hospital. At that time his only complaint was headache. Blood pressure was 136/88 mm. of Hg; pulse, 60/minute, with a prominent sinus arrhythmia; temperature, 100.2° rectal. Physical findings consisted only of right costovertebral angle tenderness. Chest x-ray revealed multiple minute calcifications in both lung fields and a cardiothoracic ratio of 14/30. Electrocardiogram was normal. Initial chemical studies (table 1) included a blood urea nitrogen of 105 mg.% and a CO_2 combining power of 11 mEq./L. Liver function tests, including bromsulphalein, thymol turbidity, cephalin flocculation, total protein, A/G ratio and serum bilirubin, were

Table 1

Blood Chemical Studies on Fifth Oliguric Day

	Milligram %			mEq./L.				HCT	W.B.C.
	B.U.N.	Creatinine	Uric Acid	Na^+	K^+	Cl^-	CO_2		
Case 1	105	21	12	130	4.6	100	11	41	14.500
Case 2	118	18	12	135	5.2	109	9	41	13.400

all within normal limits. Urine on admission was clear yellow; specific gravity, 1.002; pH, 5; protein, 3 plus; 8 to 10 white blood cells per high power field; occasional glitter cells[12] and hyaline and fatty casts. No oxalate crystals were seen, and culture showed a heavy growth of *Aerobacter aerogenes*. The patient was placed

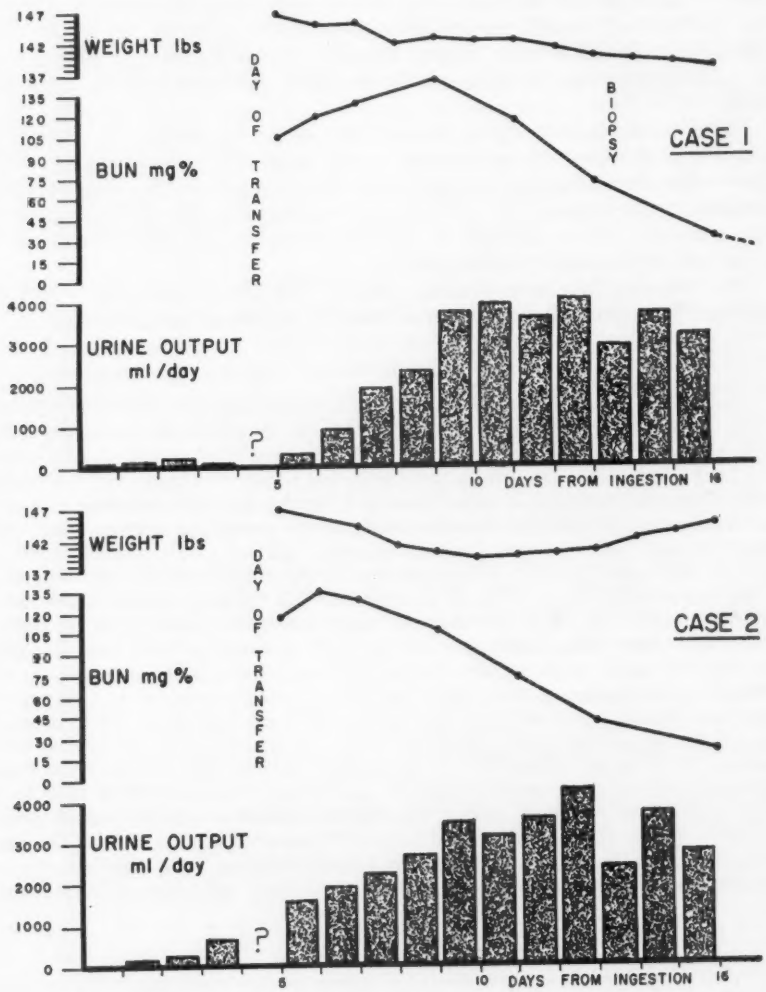

FIG. 1. Clinical course of acute renal insufficiency due to ethylene glycol.

on a regimen of fluid restriction (as previously described from this laboratory[13]). He rapidly became asymptomatic except for vomiting, which persisted until the thirteenth day. Diuresis began after six days of oliguria (figure 1). The highest blood urea nitrogen reached was 145 mg.%. A renal biopsy was performed on the

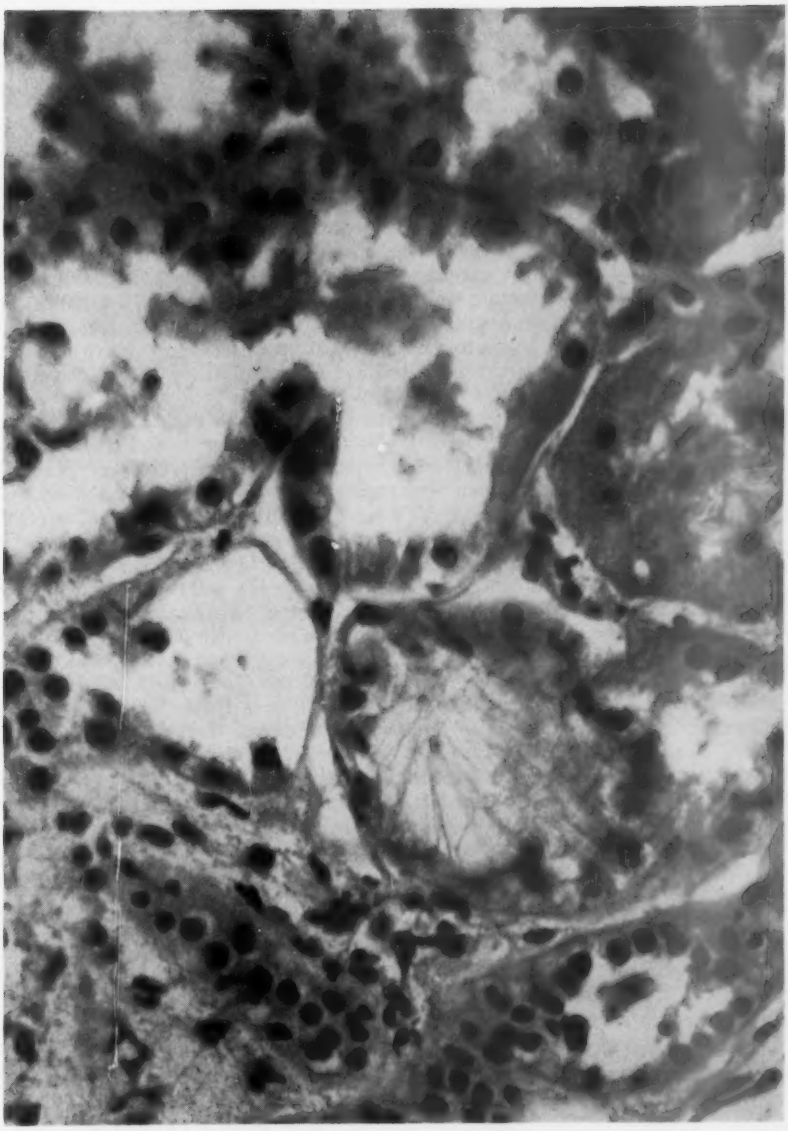

FIG. 2. Renal biopsy from a patient with acute renal insufficiency due to ethylene glycol showing the marked destruction of epithelial cells and the deposition of calcium oxalate within tubules.

fourteenth day of his illness, utilizing a percutaneous approach with a modified Vim-Silverman needle. A representative sample of cortex (figure 2) was obtained, as judged by the presence of 10 glomeruli in the section. The tissue showed marked destruction of epithelial cells, with preservation of the basement membrane, beginning regeneration in areas, and occasional tubules filled with masses of calcium oxalate crystals which flattened the epithelium at the point of contact.

On the seventeenth day of illness an endogenous creatinine clearance was 86 ml./min./1.73M^2. Maximum osmotic U/P ratio on the tenth day was 1.54. On the twenty-second day a phenolsulfonphthalein test showed 24% of dye excreted in 15 minutes, with a two-hour total of 58%. Repeat chest x-ray revealed a decrease in cardiothoracic ratio to 12/29. PPD skin test was negative, a histoplasmin skin test positive. A neurologic consultant found no evidence of residual central nervous system damage, and the patient was discharged on the twenty-fourth day of illness.

Case 2. A 16 year old white male prison inmate had ingested 70 to 90 ml. of "Zerex" on the afternoon of August 6, 1955. He noted no particular reaction for about two hours, when he began to feel numb and experienced diplopia with lightheadedness. Patient was assisted to his bed and either fell asleep or lost consciousness. The next day he got out of bed, fainted and was put back to bed. He awoke in the hospital on the third day with vomiting, pain in both flanks, and diminished urinary output. On the fourth day of illness the output rose to 650 ml./24 hours, and on the next day he was transferred to the Georgetown University Hospital. Physical examination on admission was negative except for tenderness over both kidneys. The blood pressure was 120/80 mm. of Hg. Initial chemical studies (table 1) revealed a blood urea nitrogen of 118 mg.% and a CO_2 combining power of 9 mEq./L. Chest x-ray revealed a cardiothoracic ratio of 12.5/29. Electrocardiogram and liver function tests were normal. Urine was cloudy yellow; specific gravity, 1.003; pH, 5.5; proteinuria, 2 plus. Sediment showed occasional clumps of white blood cells, with some glitter cells and broad hyaline casts. No oxalate crystals were seen. Urine culture showed *A. aerogenes, Escherichia coli* and pseudomonas. Stool guaiac was initially positive, and negative thereafter. The patient continued his diuresis (figure 2) and had an uneventful convalescence during his hospital stay. Endogenous creatinine clearance on the seventeenth day of illness was 86 ml./min./1.73M^2. Maximal osmotic U/P ratio on the thirteenth day was 1.56; phenolsulfonphthalein test showed 22% of dye excreted in 15 minutes, a total of 93% in two hours. Repeat x-rays showed a decrease in heart size, with a cardiothoracic ratio of 10.5/28.2. A neurologic consultant found no residual central nervous system damage, and the patient was discharged on the twenty-fourth day of illness.

Discussion

The course followed by these patients is noteworthy for the mildness of the central nervous system effects, which were scarcely more severe than those of a moderately heavy drinking bout. Similarly, cardiopulmonary manifestations were limited to x-ray demonstration of a decrease in heart size during convalescence, and the description of the first patient as hyperpneic on admission. These not withstanding, both patients developed an acute renal insufficiency typical of that seen following exposure to a variety of nephrotoxins and renal ischemic episodes.[14] The nausea, vomiting, flank pain, renal tenderness and acidosis [15] out of proportion to the degree of uremia are all well known manifestations of ethylene glycol poisoning. The absence of oxaluria may be a function of elapsed time. Normal liver function tests and the lack of hepatic tenderness and enlargement are in keeping with the resistance of this organ to

ethylene glycol. By way of contrast, diethylene glycol produces a severe centrilobular necrosis, and icterus has been described in the clinical picture produced by this agent.[16]

The pathogenesis of acute renal insufficiency in ethylene glycol poisoning has remained obscure, largely because the fatal cases are dead within 48 hours, a time when little more than calcium oxalate crystals are to be seen in the kidney. This has been so generally true that a recent book devoted to renal pathology [6] describes the tubular epithelium in this situation as showing "no significant degenerative or regenerative changes." In sharp contrast, the examination of renal tissue in a surviving patient provides incontrovertible evidence that the ingestion of ethylene glycol may produce widespread epithelial cell necrosis in renal tubules, with apparent preservation of basement membranes and deposition of calcium oxalate crystals in tubular lumina. This is reflected functionally in a marked impairment of active tubular water transport. Crystal deposition as a cause of the acute renal insufficiency seems most unlikely in view of their widely scattered distribution as well as the preservation of epithelium at points of contact. These crystals may be considered as an interesting but incidental finding related to the production of oxalic acid.

Tubular epithelial necrosis, on the other hand, is well established as the basic anatomic lesion in acute renal insufficiency,[17] and adequately explains most of the clinical picture observed in our two patients.

It only remains, therefore, to speculate on the relative importance of ethylene glycol as compared with its metabolic product, oxalic acid, in producing the renal lesion. In this connection it may be noted that a structurally similar compound, propylene glycol, which does not form oxalic acid, is not directly toxic to the kidney.

Oxalic acid was first implicated as the nephrotoxin of ethylene glycol poisoning 60 years ago,[5] and remains a reasonable possibility. In the experimental animal it has produced renal epithelial cell necrosis and oxalate crystal deposition,[18] a picture quite similar to that described in our first patient.

Fatal doses of oxalic acid as low as 2 gm. have been described.[18] If a rough calculation is made using the commonly accepted fatal dose of ethylene glycol (100 ml.) and the fraction converted to oxalic acid (3 to 10%), the amount derived (3 to 10 gm.) is at least in the right order of magnitude. We are not certain, however, that these speculations provide an adequate rationale for treatment aimed at neutralizing or metabolizing oxalic acid, i.e., calcium, parathyroid extract and insulin.[5]

Treatment of ethylene glycol poisoning remains, for the present, symptomatic and supportive. The measures employed correspond to the stage at which the patient is seen. In this era the course of renal insufficiency, as modified by the duration of oliguria and the magnitude of the catabolic vectors,[19] may be managed with reasonable expectation of a successful outcome.

Summary

1. Two surviving cases of acute renal insufficiency due to ethylene glycol poisoning are reported.

2. Renal needle biopsy was used to obtain the first known demonstration of the unique histologic picture of the ethylene glycol kidney in a surviving patient.

3. Ethylene glycol as "permanent type" antifreeze is an increasingly available poison which may be fatal in doses of 100 ml. or more. It produces a confusing clinical picture consisting of: (a) central nervous system effects up to 24 hours; (b) pulmonary edema and cardiac damage from 12 to 72 hours, and (c) acute renal insufficiency with oliguria and uremia in patients who survive more than two to three days.

4. Discussion centers on the pathogenesis of the renal lesion, which is nephrotoxic in type and may be due to oxalic acid formed in the metabolism of ethylene glycol.

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SUMMARIO IN INTERLINGUA

Un avantage unic del biopsia a agulia del ren es su capabilitate de demonstrar precoce alterationes histologic in inusual morbos renal. Le presente reporto constitue le prime cognoscite demonstration ante morte del ren ethyleno-glycolic in un patiente qui superviveva. Le constatationes pathologic consisteva de acute necrosis tubular del typo nephrotoxic insimul con depositos intratubular de crystallos de oxalato de calcium.

Studios clinic e laboratorial in duo masculos de 17 e 16 annos de etate qui habeva ingerite 80 ml de ethyleno-glycol (in le forma de "Zerex") revelava un bon correlation con le resultatos de biopsia renal. Le tableau clinic esseva predominatemente un tableau de acute insufficientia renal, precedite per initial manifestationes del systema nervose central e le disveloppamento subsequente de hyperpnea e cardiomegalia.

Le studio detaliate de iste casos provide le opportunitate de passar in revista le aspectos inusual de invenenamento a ethyleno-glycol e acido oxalic. Ethyleno-glycol deveni toxicologicamente de plus in plus importante in consequentia de su crescente usos industrial e commercial (como per exemplo in solutiones anticongelatori). In 1951 su production in le Statos Unite amontava a 341.000 tonnas.

Le discussion se concentra super le complexe tableau clinic de invenenamento per ethyleno-glycol e super le pathogenese del acute insufficientia renal. Es formulate le opinion que iste insufficientia non depende del formation de crystallos sed resulta del necrosis effectuate in le epithelio tubular per le glycol o su producto metabolic, oxalato.

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GENERALIZED OSTEOSCLEROSIS ASSOCIATED WITH DIABETES INSIPIDUS AND NEUROLOGIC SYMPTOMS *

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Introduction

Diffuse osteosclerosis is of varied etiology. Its pathogenesis is poorly understood. The clinical and x-ray features have become stereotyped in most cases, but do not as a rule suggest the etiology.

The conditions in which osteosclerosis, with or without hyperostosis, is seen, are:

1. Hypothyroidism.
2. Postoperative hyperparathyroidism.
3. Neoplasia, especially carcinoma of the prostate.
4. Hypervitaminosis D and, more rarely, A.
5. Fluorosis.
6. Phosphorus poisoning.

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The known causes of overgrowth of periosteal bone are:

1. Syphilis.
2. Healed scurvy.
3. Healed rickets.

The primary disorders of unknown etiology which cause increased density of bone are:

1. Paget's disease.
2. Albers-Schönberg disease (marble bones).
3. Engelmann's disease (progressive diaphyseal dysplasia).
4. Infantile cortical hyperostosis.
5. Melorheostosis.
6. Osteopoikilosis.

The following is a case of generalized osetosclerosis and hyperostosis which does not fit into any of the above categories. It is very similar to a case reported by Hinge and Menck-Thygesen in 1951.[1] This case is of further interest because of the speculation that the marked overgrowth of bone may have produced symptoms relative to the central nervous and endocrine systems.

Case Report

The patient was a 56 year old white male veteran admitted to this hospital in November, 1954. The illness had begun about 1946, when he developed difficulty with gait and weakness in the legs of a spastic type associated with pain and muscular fasciculations. He noted inability to perform fine movements and fasciculations in the muscles of the shoulder girdle. There was a tendency to fall to the right. Walking was especially difficult in the dark. Low back pain was present and was made worse by bending and stooping. There was no radiation of pain into the legs. A suboccipital headache had been noted occasionally. There had been intermittent tinnitus without vertigo or loss in hearing. By 1950 he had developed urgency, frequency, dribbling and nocturnal incontinence. Polyuria and polydipsia were present. There had been intermittent dysuria and right flank pain. In 1954 he had had no significant progression of symptoms. The renal symptoms had improved, although polyuria and polydipsia had continued.

Past history failed to reveal any evidence of diabetes mellitus. There had been no trauma to the head. The patient had been asymptomatic and in good health until about 1946. There was no indication that his stature had shown any significant change in adult life. He had had no visual disturbances. There was no history of contact with lead, phosphorus or fluorine. There was no history of syphilis. He had not ingested either vitamin A or D, apart from the amounts contained in the ordinary diet. A myelogram, done in 1950 at another institution, was unsatisfactory for technical reasons.

Family History: The patient knew no particulars of the illnesses of his parents or his five siblings. A brother has "hip trouble" and cannot walk. All siblings are said to have "large features."

Physical Examination: Blood pressure was 130/90 mm. of Hg; pulse, 72; respirations, 18; temperature, 98° F. The patient was a slightly obese, stooped individual whose stature was notable because of a large frame, superficially resembling acromegaly but lacking in the characteristic changes in hands and skull (figure 1). His mental responses were slow. The skin appeared normal. The pupils reacted normally. The funduscopic examination was within normal limits. There was no

FIG. 1.

temporal pallor of the optic discs. Gross visual field examination was normal. The tympanic membranes were intact and clear. The thyroid was not palpable. He was edentulous. The cardiovascular examination was within normal limits. Respiratory excursion was slightly diminished. There was mild increase in AP diameter, but the lung fields were normal to auscultation and percussion. The liver, spleen and

kidneys were not palpable. The genitalia were those of a normal adult male. Both testicles were of normal size. Kyphosis was marked, with some limitation of motion in the spine. Facial bones were large, but there was no prognathism. Skeletal features appeared larger than normal. Extension of the elbows was limited to 140°. Complete flexion was limited by about 15°. The neurologic examination revealed muscle fasciculations around the shoulder girdle. There was slight atrophy of muscles about the shoulder. All deep tendon reflexes were hyperactive. Mild weakness of all extremities was noted. The gait was spastic. Bilateral Hoffmann's reflexes were present. No Babinski reflex was elicited. Sustained clonus was present on the right. The sensory examination was normal. Cranial nerves were intact.

Laboratory: White blood cell count was 7,400 cells/mm^3. The differential was 59 neutrophils, 39 lymphocytes, 1 monocyte, 1 eosinophil. Hemoglobin was 16.3 gm.%; hematocrit, 44 mm.; sedimentation rate, 21 mm./hr. Urinalysis showed a specific gravity of 1.003; 20 to 25 white blood cells per high power field in clumps; rare red blood cells; albumin, negative. Urine culture showed proteus and *Aerobacter aerogenes.* The blood urea nitrogen was 12 mg.%. The calcium was 10.1 mg.%; phosphorus, 3.1 mg.%; alkaline phosphatase, 2.5 Bodansky units. Total protein was 7.1 gm.%; albumin, 4.5 gm.%; globulin, 2.6 gm.%. The blood Wassermann reaction was negative. Sodium was 154 mEq./L. (control level of 140 mEq./L.) following moderate water restriction in association with Fishberg concentration test. Specific gravity of urine at this time was 1.003. Specific gravity following Pitressin was 1.018. Fasting blood sugar was 97 mg.%.

An audiogram showed mild bilateral nerve deafness. Visual fields were normal by perimeter studies. The basal metabolic rate was plus 6. Chest x-ray showed dense skeletal structures (figure 3A). Lungs and heart appeared normal. X-rays of skull showed increased density and thickness of bone. The base of the skull was particularly affected (figure 2A). Bowen-Hirtz views of the skull demonstrated a foramen magnum "smaller than is usually seen." Bone survey showed all bones to be of increased density and width. Lumbar vertebrae were massive (figure 3B). Severe degenerative arthritis of the spine was present, with spurring and calcification of ligaments. The radius, ulna, tibia and fibula showed marked periosteal proliferation, with exostoses appearing as "dripping candle wax" (figure 2B). The sella turcica was normal. Intravenous pyelogram revealed a moderately dilated right renal pelvis and upper ureter. The left kidney and ureter were normal.

Hospital Course: The patient was cystoscoped and found to have an atonic bladder with 1,200 c.c. of residual urine. There was sensory loss along the urethra and in the bladder wall. The prostate was normal. The impression was that this was a neurogenic bladder.

Bone biopsy and bone marrow examinations were normal. Lumbar puncture could not be accomplished because of changes in the vertebrae, ligaments and interspaces. Open myelography was not attempted.

Nasal insufflation of posterior pituitary extract had a partial effect on renal symptoms, especially polyuria, but the patient continued to have frequency and overflow incontinence. It was not possible to clear the urine of pathogens because of the neurogenic bladder. Symptomatically the patient remained the same throughout his hospital stay.

Comment

The abnormal skeletal growth seen in this patient must have begun many years ago. The symptoms have been stationary for at least four years, suggesting some stabilization of the disease. A biopsy of the ilium showed micro-

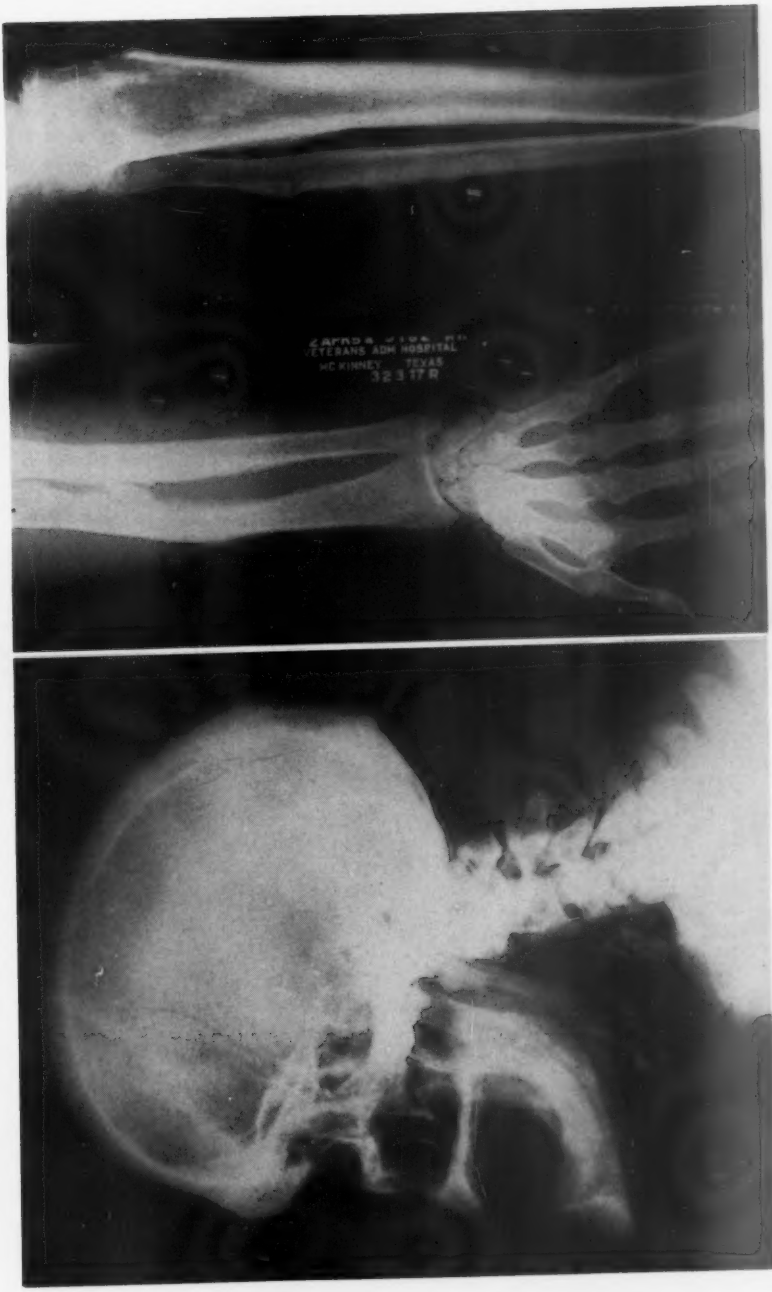
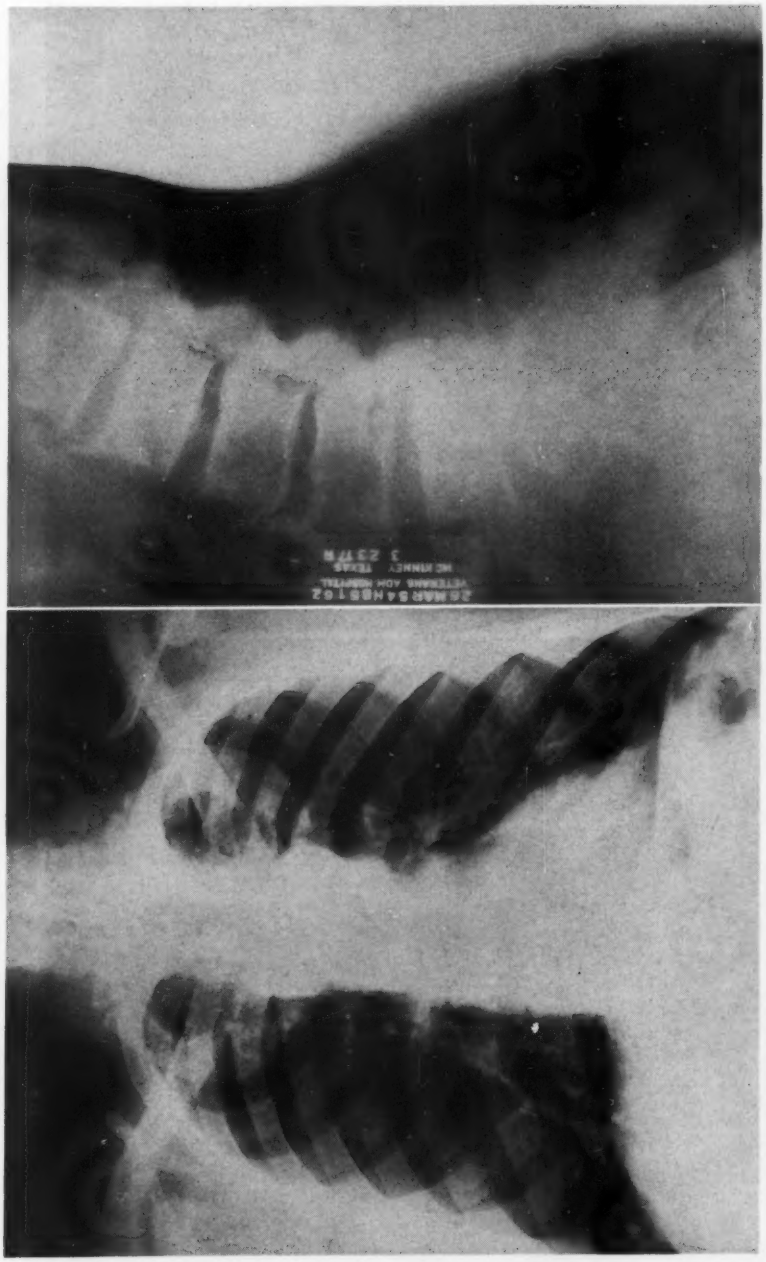


FIG. 2.



B

A

FIG. 3.

scopically normal bone. Blood chemical studies were normal. There was no evidence of significant encroachment upon the marrow cavity.

The neurologic picture was very suggestive of amyotrophic lateral sclerosis. However, it is conceivable that cord compression might result in findings of bilateral spasticity and mild weakness. Of interest in this connection is the work of Mellanby, who reported on skeletal changes produced in young dogs by diets deficient in vitamin A.[2] Overgrowth of bone was noted generally but was most pronounced in the posterior base of the skull, the petrous ridge and the vertebral column. These changes resulted in diminished size of the cranial vault, compression of cranial nerves and compression of the fourth ventricle and aqueduct. Inward growth of vertebrae caused cord compression. Central nervous system degeneration was most severe between midbrain and C_6 in these animals. Posterior roots were usually affected. Anterior roots sometimes escaped. It seems likely that, in this case, overgrowth of bone might have similarly affected the nervous system.

The diagnosis of diabetes insipidus seems definite. Hyperosmolar electrolyte concentration developed on water restriction. The low specific gravity responded only to Pitressin. Although the sella turcica appeared of normal size on x-ray, one wonders whether this lesion might not have resulted from the thickening and sclerosis of the base of the skull affecting the hypothalamic-pituitary axis.

The patient's brother was investigated to determine the nature of his "hip disease." He was found to have almost complete fixation of both hip joints. His age is 61 years. Symptoms referable to the hips were first noted five years ago. X-rays of his hips showed marked degenerative change and sclerosis about the head of the femur and acetabulum (figure 4). The cause of these changes is not known. They are similar to those seen in Legg-Calvé-Perthes' disease and familial coxitis. A sister 59 years of age was investigated and found to be normal. No other siblings could be studied.

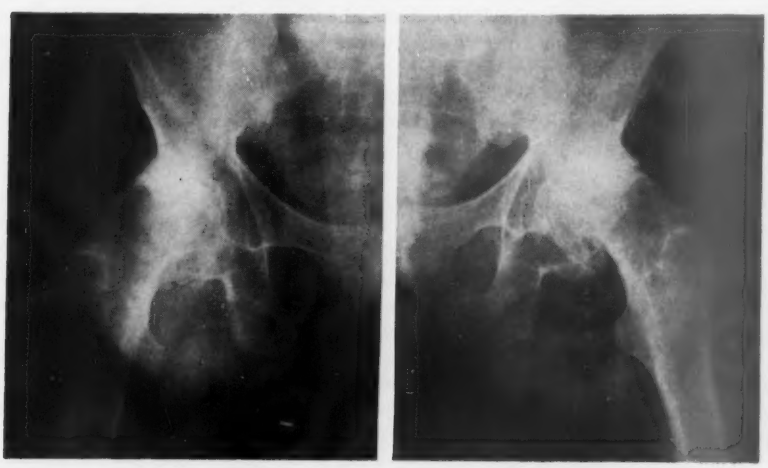


FIG. 4.

Discussion

The abnormality of bone in this case is ill-defined. The massive size of the skeleton, the generalized osteosclerosis and the periosteal proliferation do not fit into accepted classifications. Comparison with a case of Hinge and Menck-Thygesen [1] is rather close. Paresis of the left abducens nerve was the only neurologic lesion described in their case. They too were unable to classify the abnormality or to suggest any possible etiology.

The differential diagnosis included the causes of osteosclerosis. None of them is acceptable as a diagnosis. Paget's disease [3] is not a generalized disease of bone. The characteristic mosaic pattern of bone seen in Paget's disease was not present. The blood chemical findings of Paget's disease were absent in this case.

"Marble bones," or osteopetrosis (Albers-Schönberg disease),[4, 5] is a familial disease of bone causing generalized osteosclerosis, loss of normal osseous structure, and decrease in size of marrow cavity. The metaphysis is particularly affected and is often clubbed.[6] Transverse bands may be seen at the metaphysis similar to those resulting from the effects of bismuth, lead and phosphorus. The shape and size of bone are otherwise unaffected. Fragility of bone may or may not be present. Splenomegaly and hepatomegaly develop when encroachment upon the marrow cavity is significant. Blood chemical studies are normal. The features of the case here described are not sufficiently similar even to the "benign form" [5] to warrant a diagnosis of osteopetrosis.

Fluorosis [5, 7] causes a generalized increase in density of bone and ligaments without affecting shape of bone. Most cases described have been in cryolite workers. Fluorine osteosclerosis has been described as originating from drinking water in India.[7] Drinking water in the United States does not contain sufficient fluorine to produce this disorder.[8] In this case the marked increase in density of bone, the increase in size, the thickening and sclerosis of the base of the skull and lack of history of contact are all against the diagnosis of fluorosis.

Melorheostosis of Leri [9, 10, 11] affects the outer contour of bone only, is asymmetric and is not a cause of generalized osteosclerosis. The case reported by Franklin and Matheson [9] is frequently referred to in the literature. It does not in any way compare with the present case.

Engelmann's disease,[5, 12] or progressive diaphyseal dysplasia, produces sclerosis and loss of trabeculation primarily of the shafts of the long bones and base of the skull. The disorder is symmetric and is associated with new bone formation of both endosteum and periosteum. Hands, feet, spine and pelvis are not affected.[14] This is usually discovered in childhood, but cases have been described in individuals aged 24,[12] 28 [13] and 34 years.[15]

Osteopoikilosis is a localized disorder of bone giving rise in the x-ray to a "polka-dot" appearance of bone due to islets of osteosclerosis. It is a familial disease.

Infantile cortical hyperostosis [16] is a painful, febrile illness involving periosteal proliferation during the first year of life. The disorder needs to be differentiated from periostitis of congenital syphilis and scurvy. The process resolves spontaneously at about two years of age.

Neoplastic disease of bone in carcinoma of prostate,[17] leukemia [18] and even multiple myeloma [19] have produced more or less generalized forms of osteo-

sclerosis. None of these disorders was present in this case. The problem here is not one of osteomyelosclerosis.

Summary

A most unusual case of generalized osteosclerosis is reported. The etiology is not apparent. A review of the literature has failed to reveal a satisfactory diagnosis in this particular case. It is believed that the overgrowth of vertebrae and base of skull produced the neurologic lesion described and diabetes insipidus.

Summario in Interlingua

Diffuse osteosclerosis ha varie etiologias. Le cognoscite causas de osteosclerosis, con o sin hyperostosis, es hypothyroidismo, hyperparathyroidismo post-operatori, neoplasia (specialmente carcinoma del prostata), hypervitaminosis D e A, fluorosis, e invenenamento a phosphoro. Le cognoscite causas de hypercrescentia ossee es syphilis, scorbuto curate, e rachitis curate. Le disordines primari de non-cognoscite etiologia que causa augmentate densitate ossee es morbo de Paget, infantil hyperostosis cortical, melorheostosis, e osteopoicilosis.

Le caso hic presentate non es classificabile in le categorias mentionate. Il se tracta de un masculo blanc de 56 annos de etate con osteosclerosis generalisate, hyperostosis, e augmento del largor de osso. Su gravamines esseva concernite con debilitate del gambas e con dolores in le gambas non associate con effortio. In marchar ille cadeva facilemente. Su ambulatura esseva spastic. Ille non poteva executar movimentos delicate con su manos. Iste symptomas habeva progredite durante le passate octo annos.

Le examine physic revelava atrophia muscular in le cinctura scapular. Fasciculationes muscular esseva presente. Le reflexos esseva hyperactive. Debilitate in omne extremitates esseva notate. Le ambulatura esseva spastic. Bilateral reflexos de Hoffmann esseva presente. Persistente clono al latere dextere esseva presente. Le examine sensori esseva normal.

Le manifestationes neurologic del morbo esseva compatibile con sclerosis lateral amyotrophic, sed le possibilitate esseva prendite in consideration que iste lesion esseva secundari a un compression del medulla spinal causate per le marcate excesso de crescentia e le hypertrophia del vertebras e forsan un restriction del foramine magne. Esseva monstrate que le patiente habeva diabete insipide, e le speculation esseva que isto esseva causate per le marcate sclerosis del base del cranio, con alterationes secundari in le glandula pituitari.

Le presente caso esseva considerate como extraordinarissime. Un revista del litteratura non produceva un diagnose satisfactori pro iste caso specific de osteosclerosis. Esseva postulate que le hypercrescentia del vertebras e del base del cranio produceva le describite lesiones neurologic e etiam le diabete insipide.

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AGAMMAGLOBULINEMIA IN ADULTS*

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The purpose of this report is to call attention to another case of agammaglobulinemia in an adult, to emphasize a few of the features of this interesting process, and to add to the accumulating data with respect to its association with various relatively common pathologic processes.

Case Report

A 38 year old white male clerk was admitted to Grand View Hospital May 29, 1954, with an 18 month history of recurrent episodes of fever, chills, sweats, coughs, expectoration, bilateral anterior chest pain and weakness.

As a child he had apparently had good health, having had only measles. At about the age of 21 he began having prolonged attacks of colds, each associated with

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nasal stuffiness, nasal discharge and general weakness and fatigue. At times these symptoms continued throughout an entire winter. In November, 1939, following a severe cold, he developed a purulent drainage from both ears which lasted approximately three months. During the following two winters each cold was associated with a discharge from his ears. Thereafter, however, he had no further difficulties with ear infections. He remained fairly well until 1947, during which year he had considerable difficulty with recurrent severe head and chest colds, occasionally associated with abdominal pain, nausea, vomiting, chills and fever. He gradually regained his weight and the symptoms abated.

From June through August, 1952, he suffered in much the same way as he had during the year 1947. In November, 1952, following a prolonged cold, he developed his first attack of high fever associated with severe chest pain, nausea and nasal discharge. A chest x-ray was said to have shown evidence of "pleurisy." He made a gradual recovery with penicillin treatment. One month later he had a similar episode of chills, fever and chest pain, this time associated with considerable cough and expectoration lasting several weeks in spite of penicillin treatment. In August, 1953, he had his third major episode of chills, fever, chest pain, cough and expectoration. At that time he had chest and sinus x-rays taken at an osteopathic hospital, where it was felt that a "chronic sinus condition had resulted in drainage into and irritation of his lungs." For this he was given four x-ray treatments to his sinuses, in addition to treatment with iron, liver, B_{12} and vitamins. At about this time an enlarged spleen was also discovered, and he was advised not to work for at least one month. During the early months of 1954 he had a series of attacks, always coming suddenly, with tiredness, fever up to 104° F., anterior chest pains, cough, expectoration, nasal discharge and vomiting. During this time he was given various antibiotics. In February, 1954, chest x-ray and a bronchoscopic examination were done at the osteopathic hospital. The chest film was said to have shown "inflammation" in both lungs, and the bronchoscopic examination was reported as "favorable." In March, 1954, he received a course of cortisone treatment which made him feel somewhat better. A final, similar febrile episode, in May, 1954, prompted his first hospital admission. He reported a loss of approximately 20 pounds in weight.

Physical examination on admission to the hospital showed a pale, poorly nourished and chronically ill adult male. The temperature was 101° F.; pulse, 100; blood pressure, 120/80 mm. of Hg; weight, 120 pounds. No significant abnormalities of the ears, nose and throat were noted. There was no lymphadenopathy. The chest exhibited equal expansion bilaterally and was resonant throughout. Breath sounds were slightly diminished over the right midlung field posteriorly. No râles or rhonchi were heard. The heart appeared normal and no murmurs were audible. The liver edge was just barely palpable and was nontender. The spleen was easily felt below the left costal margin. There was moderate clubbing of all the fingers.

Studies on admission revealed the following: hemoglobin 13.0 gm.; red blood cells, 4,030,000; white blood cells, 10,500, with 91% neutrophils, 8% lymphocytes and 1% monocytes. Urinalysis showed specific gravity, 1.015; albumin, 2 plus; 12 to 20 white blood cells per high power field. The erythrocyte sedimentation rate was 58 mm. in one hour. The fasting blood sugar was 113 mg.%; blood urea nitrogen, 10 mg.%; blood serologic test for syphilis, negative; serum bilirubin, 1.3 mg.%; total serum proteins, 4.5 gm.%, with albumin, 3.6 gm.%, and globulin, 0.9 gm.%. The prothrombin time was 19 sec. (control, 15 sec.). The thymol turbidity was negative in 24 hours; cephalin flocculation 2 plus in 48 hours. A bromsulfalein test showed no dye retention in one hour. An electrocardiogram was normal. A chest x-ray showed abnormal density involving the lower medial portion of the right lung, with a more diffuse similar involvement of the left lower lobe. Febrile

agglutination tests for typhoid, paratyphoid, proteus and brucella were all negative. A sputum culture showed principally gram-positive diplococci. Sputum smears and culture for acid-fast organisms were negative. Sputum culture was also negative for fungi. Several blood cultures were negative. Tuberculin tests with first and second strength PPD were negative, as were the histoplasmin and coccidioidin skin tests. Serologic tests were negative for histoplasmosis, coccidioidomycosis, blastomycosis, influenza A and B, Q fever and the psittacosis-lymphogranuloma venereum group. A Congo red test showed disappearance of 37.5% of the dye in one hour. A repeat total serum protein was 5.2 gm.%, with albumin, 3.95 gm.%, and globulin, 1.25 gm.%.

The patient's hospital course was complicated on the third day by a temperature rise to 105° F. with tachycardia, severe shaking chills, cough and expectoration of bloody sputum. He developed dullness, bronchial breathing and egophony at the left base posteriorly. A white blood count was 20,550, with 93% neutrophils. A repeat chest x-ray showed a marked change in the appearance of the left base, with a diffuse and rather uniform increase in density. On the second day of sustained fever (104° to 105° F.) he was started on large doses of penicillin intravenously and intramuscularly. Within 24 hours his temperature dropped to normal and remained so during the following 11 days of his hospital stay. His symptoms likewise improved rapidly, but he continued to show signs of consolidation over the left lower lobe. He was maintained on penicillin therapy, and on June 12, 1954, was transferred to the Barton Division of Jefferson Hospital.

Further studies were directed principally toward the lungs. The spleen was no longer palpable, and the patient was asymptomatic with the exception of cough and expectoration. X-ray on admission showed the right lung to have cleared with the exception of "prominent bronchovascular markings." There was residual density in the posterior basilar region of the lower lobe which failed to clear further. The physical signs, however, were out of proportion to the extent and character of the x-ray findings. Persistent dullness, bronchial breathing and whispering pectoriloquy were heard at the left base posteriorly up to the angle of the scapula. The bronchogram, however, was reported normal. Laboratory studies showed total protein of 5.72; albumin, 5.12, and globulin, 0.6 gm.%. The significance of the low globulin was not appreciated at the time. The leukocyte count was almost normal, and the urine no longer showed albumin.

The failure of the physical signs to clear, and the density on x-ray, led to the suspicion of a chronic nontuberculous pulmonary disease, and surgery was advised.

At operation by Dr. George Willauer the left lower lobe was consolidated completely except for the anterior basal segment and the very tip of the superior segment. The lingula was also consolidated. Many large glands were noted in the inferior pulmonary ligament. The lower lobe and tip of the lingula were resected. The patient's postoperative recovery was normal and complete. Pathologically, the bronchial tree was dilated proximally. The consolidated area was reported as showing "organizing pneumonia."

The patient was discharged from the hospital on the eleventh postoperative day. A few days later the possibility of the true state of affairs was recognized upon the appearance of the first report of agammaglobulinemia in an adult, by Sanford et al.[1] Electrophoretic study by Dr. F. W. Sunderman confirmed our impression (figure 1A). The gamma globulin was barely detectable. Furthermore, a test for isohemagglutinins by Dr. L. A. Erf was entirely negative.

In view of the fact that early observers [2] felt that therapy with gamma globulin could remedy the defect, the patient was treated with monthly injections amounting to 36 c.c. of pooled gamma globulin. His progress has been better than before but not entirely satisfactory, and it has been necessary to employ antibiotics on two

occasions. However, he has lost very little time from his employment, and it is believed that the gamma globulin injection was helpful. To determine whether it produced a measurable increase in the gamma globulin in the electrophoretogram, the study was repeated eight days following an injection (figure 1B), and although the level was slightly higher, it was not certain that the increase could be ascribed to the treatment. Further management of this patient will depend upon development of our knowledge of the problem.

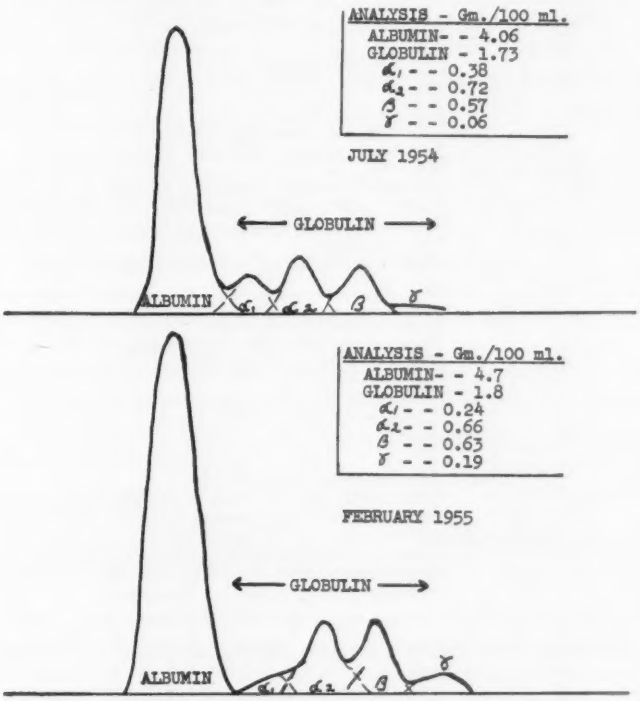

FIG. 1. A—above; B—below.

COMMENT

This patient shows many of the features found in reported cases of agammaglobulinemia. He had recurrent chronic respiratory infection, both upper and lower, difficulty in clearing his lungs of consolidation, splenomegaly, lymph node enlargement and general debility. Bronchiectasis, so common in reported cases,[1, 4] was not found, probably because insufficient time had elapsed since the onset of chronic pulmonary disease. The portion of lung most likely to develop it was resected.

Table 1 summarizes the clinical features of reported cases in adults. It will be noted that there is approximately equal sex incidence, and that most appear

in the third or fourth decade. (Since most of these had had trouble for some years, it is likely that the majority of patients began with trouble during the second or third decade.) Susceptibility to infection, especially respiratory infection, is the most common characteristic among these patients. There was only one exception,[5] and in that patient the syndrome of hypersplenism and reticulum cell hyperplasia was outstanding. This has occurred in other patients as well. The spruelike syndrome was present in two of the summarized cases.[1, 7]

TABLE 1

Clinical Features

Sanford et al.[1]		39 F. Chronic respiratory infections since age 17. Spruelike syndrome since age 23. Meningitis, multiple abscesses, bronchiectasis.
Prasad and Koza[3]		30 F. Meningitis, frequent attacks of pneumonia. Banti's syndrome—hypersplenism—splenectomy (granuloma formation in sections of spleen) Polyarthritis. Normal sedimentation rate (one exception in 21).
Zinneman et al.[4]	1.	29 M. Recurrent pneumonia—bronchiectasis—resection. Two episodes of pneumonia during gamma globulin therapy. Maintained on antibiotic therapy
	2.	37 M. Pneumonia, recurrent respiratory infection. Continues to have chronic pulmonary lesion with fibrosis
Rohm et al.[5]		29 F. Hypersplenism—splenectomy. Spleen and lymphatic tissue showed fibrosis, lymphopenia and reticulum cell hyperplasia
Grant and Wallace[6]		17 F. Three attacks of whooping cough, seven of pneumonia. Splenomegaly and neutropenia even during attack of pneumonia.
Wall and Saslaw[7]	1.	26 M. Cleft palate and congenital hip dislocation in childhood. Erysipelas. No recurrent infections until age 26. Pneumonias.
	2.	40 M. Lymph node biopsy showed reticulum cell hyperplasia. Recurrent pharyngitis. Prolonged diarrhea, spruelike syndrome. Purulent bronchitis, "slight" hepatosplenomegaly.

The abnormalities of plasma proteins in these cases are fairly regular. Each shows a normal plasma albumin. The total globulin varies from a very low value to one within normal limits. In our patient there was a slight increase in the alpha 2 and beta globulin on one occasion. The presence of a normal total globulin does not rule out agammaglobulinemia, although in most cases the total value has been below normal (as in our case). As suggested by the changing total globulin figures, ranging from 0.6 gm. to 1.73 gm., clinical factors may influence this value.

Discussion

The designation of the condition described here as agammaglobulinemia, while not strictly accurate, is probably to be preferred to the term "hypogammaglobulinemia," because it constitutes a clinical entity. This is in contradistinction to the depletion of gamma globulin which occurs in various diseases, especially in patients debilitated by prolonged illnesses.[8] The latter is better referred to as hypogammaglobulinemia. One must therefore bear in mind that the term "agammaglobulinemia," as applied to the adult form of the disease, allows for the presence of detectable quantities of gamma globulin and does not imply a total absence at all times. This accords with the studies published by Craig, Janeway et al.[9, 10]

Diseases related to derangements of plasma proteins, especially gamma globulin, have been identified only recently. The syndrome of "idiopathic-dysproteinemia" was first described by Hamburger and Petermann in 1949 [11] as part of a study of hypoproteinemia. Since then several separate entities have been described, among them the specific abnormalities of gamma globulin. To date these appear to fall within the following categories:

1. Congenital agammaglobulinemia.
2. Acquired or adult agammaglobulinemia.
3. Idiopathic dysgammaglobulinemia.
4. Dysgammaglobulinemia with multiple myeloma.
5. Hypergammaglobulinemia with formation of defective antibodies.

The congenital type which appears in infants and children has been exhaustively studied from the standpoint of origin, function and identification of gamma globulin.[2, 9] In this type the ability to manufacture protective antibodies is lacking from birth and the defect appears early in life. The acquired, or adult, type is also probably a hereditary disease. In common with the congenital form, it has the defect in protective antibodies constituted in the gamma globulin, and the inability to manufacture them in response to natural and antigenic stimulation. Some have regarded this as a failure of lymphocyte function,[5] but Good [12] and others [9] have determined that in response to antigenic stimulation, vigorous maturation of the hematopoietic reticulum occurs along plasma cell lines. This does not occur in agammaglobulinemia.

One adult female [12] had extensive proliferation of free and fixed reticulum cells in the spleen, lymph nodes and bone marrow, together with granuloma formation in the spleen and lymph nodes. However, plasma cell maturation did not occur. Craig, Gitlin and Jewett [9] reported on cellular responses to injected antigens in normal, as compared with agammaglobulinemic, children. In normal children, a few weeks after the injection of triple antigen the lymph follicles showed increase in the breadth and cellularity of the nodal cortex and development of follicles having active germinal centers. Medullary cords were increased, and many plasma and preplasma cells appeared. Specific antibodies for tetanus and diphtheria toxins could be found in the plasma cells by the fluorescent antibody technic. In agammaglobulinemia the reticulum cells of the nodal sinusoids were swollen, but none of the specific changes took place.

Young and Wolfson [13] have described the cases of four adult males with agammaglobulinemia which suggested that lymphocytes have a part in the manu-

facture of antibodies. One of their patients was designated as "familial non-lymphopenic dysglobulinemia," since normal lymph nodes and lymphocytes were found. Relatives of this patient showed hypergammaglobulinemia, suggesting a hereditary defect with multiple potentialities. Their other patients had lymphopenia and were designated as "familial lymphopenic agammaglobulinemia." One patient had no circulating eosinophils, leading to the suspicion that the pituitary-adrenal axis has some bearing on gamma globulin formation. This was ruled out by Good and Kelley,[14] who demonstrated normal adrenal cortical function in patients with agammaglobulinemia. They demonstrated no consistent abnormality of lymphocytes or eosinophils, and found a normal drop in the number of circulating eosinophils following injection of ACTH in four patients. In the same patients an increase in the excretion of 11 hydroxycorticosteroids of normal magnitude resulted from ACTH injection. The role of lymphocytes in the production of gamma globulin is not clear. Plasma cells have been shown to have a definite role in the reports cited. Good [12] reports a normal liver biopsy in one of his patients, and regards this as evidence that liver abnormality is not the cause of failure of globulin synthesis.

Several reports have appeared indicating unusual leukocytosis in response to infection. One seven year old boy [15] was found to have cyclic neutropenia and agammaglobulinemia dating from the age of eight months. The gamma globulin was regularly below 0.2 gm./100 ml. and the neutropenic cycles lasted about 10 days.

The entity of hypergammaglobulinemia is interesting. The clinical features of severe recurrent and chronic nonspecific infection with hepatosplenomegaly and generalized lymphadenopathy were similar to those of patients with agammaglobulinemia, but these patients were found to have excessive amounts of gamma globulin, ranging from 1.9 to 4.5 gm./100 ml. Two of these were siblings. The authors [10] investigated patients with bronchiectasis, pancreatic fibrosis and chronic pulmonary infections, and did not find the exaggerated gamma globulin noted in these cases. R. Good reported having studied four such cases and T. Good three cases, and the former believes that the bone marrow in such patients is characterized by excessive numbers of plasma cells. He states that these patients, in company with multiple myeloma patients, have a dysgammaglobulinemia with the formation of abnormal or incomplete antibodies. We have had electrophoretic studies on a seven year old boy with typical pancreatic fibrosis and progressive cystic pulmonary fibrosis and found high gamma globulin. The value was 2.3 gm./100 ml., with total globulin of 4.6 gm./100 ml. Most likely this is an expression of the reaction to chronic infection, and does not imply a relation to the hypergammaglobulinemia syndrome referred to above.

The plasma protein distribution in patients with multiple myeloma is interesting. Reiner and Stern [16] have found that 78% of 91 patients showed a major anomaly of the electrophoretic pattern, 6.6% in the alpha range, 15.4% in the beta and 55% in the gamma fraction. Brownell [17] found hyperglobulinemia in 52% of 61 cases. Fractionation, although not performed in all cases, revealed a breakdown similar to the cases of Reiner and Stern. Cryoglobulinemia was found in one case and was associated with a high gamma globulin level. There appears to be agreement among many observers that the protein defects in mul-

tiple myeloma relate to production of abnormal antibodies by the excessive number of plasma cells.

The treatment of agammaglobulinemia in adults is unsatisfactory. Bruton [2] believed it possible to replace adequately the gamma globulin by monthly injections in children. Others have failed to protect adults from infection in this manner. Our own study suggests that the level of gamma globulin may be raised slightly by injection of pooled gamma globulin, but this slight rise may not be significant in protecting the patient from infection. Certainly the maintenance of gamma globulin at or near normal levels would require prohibitive amounts of pooled gamma globulin. For the present it is our view that it is desirable to give gamma globulin during times when exposure to infections is most likely, and to rely upon antibiotic prophylaxis and treatment for further protection.

It was our original purpose to draw attention to the possible relation of chronic pulmonary disease to gamma globulin abnormalities, but recently developed knowledge has suggested many other lines of investigation. On the clinical side, the reporting of several cases from a single locality suggests that agammaglobulinemia is not rare and that, if suspected, diagnosis can be made by appropriate globulin fractionation. Cases of bronchiectasis, spruelike syndrome, chronic recurrent infections, obscure problems of reticuloendothelial hyperplasia and related syndromes come to mind. Further, other poorly understood ailments may be found to relate to the broader field of globulin abnormality, for example, the hyperglobulinemia of sarcoidosis. Is it possible that the phenomena of "periodic disease" described by Reimann [18] (cyclic abdominal pain, arthralgia and neutropenia, and the like) relate to globulin abnormalities? Since antigen-antibody reactions are implicated in the "collagen diseases," is it possible that qualitative gamma globulin defects are implicated? These are only a few of the questions which arise in the consideration of this interesting phenomenon.

Summary and Conclusions

Another case of agammaglobulinemia is reported. This appears to follow many of the characteristics established by reports of cases during the last year. Since a number of these reports arose from limited geographic areas, it is suggested that the condition may be of more common occurrence than the rarity of reports would indicate. The condition should particularly be suspected in institutions dealing with chronic illness, especially chronic respiratory disease. Since the methods of detection are not difficult, the awareness of the possibility of the presence of agammaglobulinemia in the chronic illnesses discussed in the text should lead to its diagnosis.

Some of the further possible implications of the disease have been discussed. These may include various clinical and hematologic entities. The relationship between various globulin abnormalities is still obscure, but further study is likely to throw more light on the matter. It is entirely possible that there exists some common factor, either genetic or otherwise, which accounts for hypergammaglobulinemia in one instance and agammaglobulinemia under other circumstances.

SUMMARIO IN INTERLINGUA

Es reportate le caso de un masculo de 38 annos de etate in qui nulle globulina gamma esseva trovate in le sero. Le patiente habeva un historia de recurrente infectiones marcate per su incapacitate de reager in un maniera normal. In le curso de su vita adulte ille habeva habite plure tal periodos con infectiones respiratori, sed nulle de istos habeva essite tanto serie como le episodios occurrente durante le ultime anno e medie ante le studio hospitalari. Durante iste intervallo ille habeva a pena potite persequer su labores professional. Finalmente ille disveloppava pneumonia migrante e recurrente que non respondeva completemente a un curso de tractamento antibiotic e se organisava in su lobo sinistro-inferior. A causa del non-resolution un intervention chirurgic esseva necessari, e il esseva solmente post le restablimento del patiente ab le operation que su agammaglobulinemia esseva discoperite. In tres tests ille habeva basse nivellos de proteina sanguinee: le albumina esseva satis normal, e le globulina variava inter 0,6 e 1,25 g per 100 ml. Post le publication del prime reporto de un caso adulte de agammaglobulinemia, le sero del patiente esseva subjicite a un analyse electrophoretic, e nulle globulina gamma esseva trovate.

Un curso de tractamento con injectiones mensual de globulina gamma collectanee ha essite sequite durante le passate anno. Le patiente es multo meliorate, sed subsequente analyses electrophoretic ha demonstrate nulle significative alteration in le stato de su globulina gamma. Durante le menses de hiberno, antibioticos esseva usate prophylacticamente. Le condition del patiente remane satisfactori. Le efficacia de tractamentos a globulina gamma in adultos es non ancora definitemente establite.

Depost le prime reporto de iste condition in un patiente adulte, un numero de casos ha essite describite. Isto pare indicar que le condition non es rar e que illo debe esser prendite in consideration in patientes con infectiones recurrente. In plus, plure patientes ha exhibite un syndrome simile a sprue, e alteres ha habite splenomegalia. Le ramificationes del problema continua complexificar se.

Il ha essite proponite que lymphocytos e plasmocytos debe esser considerate como le cellulas responsabile pro le formation del globulinas sanguinee. Datos ab recente studios pare indicar que le globulinas gamma que es responsabile pro le protection del organismo contra infectiones bacterial es formate per le plasmocytos.

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EDITORIAL

THE RESPONSIBILITIES OF THE MEDICAL PROFESSION IN THE USE OF X-RAYS AND OTHER IONIZING RADIATION

Statement by the United Nations Scientific Committee on the Effects of Atomic Radiation

I. Introduction

1. The United Nations General Assembly, being aware of the problems in public health that are created by the developments of atomic energy, established a Scientific Committee on the Effects of Atomic Radiation. This Committee has considered that one of its most urgent tasks was to collect as much information as possible on the amount of radiation to which man is exposed today, and on the effects of this radiation. Since it has become evident that radiation due to diagnostic radiology and to radio-therapy constitutes a substantial proportion of the total radiation received by the human race, the Committee considers it desirable to draw attention to information that has been obtained on this subject.

2. Modern medicine has contributed to the control of many diseases and has substantially prolonged the span of human life. These results have depended in part on the use of radiation in the detection, diagnosis and treatment of disease. There are, however, few examples of scientific progress that are not attended by some disadvantages, however slight. It is desirable therefore to review objectively the possible present or future consequences of increased irradiation of populations which result from these medical applications of radiation.

II. General Survey of the Irradiation of Human Beings

3. Man has always been exposed to some irradiation from natural sources. To this has now been added, as a result of modern discoveries and the applications of ionizing radiation and radioactivity, certain forms of artificial irradiation. . . .

4. *Natural irradiation* is due to:

(1) Cosmic radiation,
(2) "Background" gamma radiation from radioactive substances present locally in the earth, rock or building materials, and from disintegration products of radon in air,
(3) Radiations emitted from natural radioelements such as potassium 40, radium, radon and carbon 14 which are incorporated in the body.

5. The amount of this natural radiation varies with locality, but has been estimated as usually delivering between 70 and 170 mrems per year to the

gonads. Of this total, the major contributions are of about 45% from local gamma radiations, 30% from cosmic rays and 20% from body potassium 40.[1]

6. *Artificial irradiation* is derived from:

(1) The contamination of the environment, the atmosphere, or water by radioactive waste from atomic industries or from users of radioelements;

(2) The radioactive fallout, at greater or lesser distances from the source, or radioactivity resulting from the explosion of nuclear devices;

(3) The occupational exposure of certain groups of workers: medical practitioners, radiologists, dentists, nurses, atomic energy workers, uranium or thorium miners, and the industrial or scientific users of radiation generators or radioactive isotopes;

(4) The medical use of x-rays, other ionizing radiations and radioelements in the detection, diagnosis, investigation and treatment of human diseases;

(5) The use of certain devices which emit radiation, such as television receivers, watches with luminous dials, and the x-ray generators used for the purpose of fitting shoes.

7. The amount of artificial radiation must vary considerably in different countries and we have inadequate information as to the over-all significance of these factors. In certain countries where estimates have been made, it appears that the greatest gonad irradiation of the population is due to diagnostic radiological procedures, the amount from this source about equalling that from all natural sources in certain instances. The total present contribution from occupational exposure, from the products of atomic industries, from radiotherapy and from the radiating devices mentioned above (paragraph 6, sub-paragraph 5) is likely to be very considerably smaller. That from radioactive fallout to the gonads appears at present to be in the region of 1% of the natural gonad irradiation in most areas.[2]

8. Both the magnitude and the significance of these various sources are under review by the Committee. Since medical irradiation accounts for a substantial if not the major proportion of all artificial exposure, it is important that its magnitude should be known accurately for different countries and circumstances. The possibility of making such an assessment depends upon the help of the medical profession, and particularly on the adequacy and availability of records kept by doctors, dentists and organizations responsible for the use of ionizing radiation.

[1] From reports sent by India, Sweden, the United Kingdom and the United States of America.

[2] According to the reports sent by the United Kingdom and the United States of America.

III. Radiation Hazards

9. The medical use of radiation is clearly of the utmost value in the prevention, diagnosis, investigation and treatment of human disease, but the possible effects of this irradiation of individuals require examination.

10. Generally speaking, the irradiation of living beings may produce radiobiological effects either on the irradiated individual himself or, through him, on his descendants; the former being termed somatic and the latter genetic effects. Somatic effects vary according to the different organs or tissues affected, and range from slight and reversible disturbances such as cutaneous erythema to the induction of leukemia or of other malignant diseases. The possible reversibility of the somatic effects of radiation received in small doses or at low dose rates encourages the belief that there are permissible doses of radiation which will not cause completely irreversible or significant somatic damage. The threshold for occasional somatic damage may, however, prove to be low. In the case of genetic effects, on the other hand, there may be no threshold. These effects increase with a frequency corresponding to the total amount of radiation received by the germinal tissues, and in the great majority of cases, are adverse.

11. Many other factors complicate the interpretation of radiobiological effects. The differences between whole and partial body radiation, between a single exposure and continuous irradiation, or between the effects of different types of radiation are still imperfectly understood. Biological differences in the radiosensitivity of various tissues, or of the tissues of people of different age or sex, obviously influence the nature of radiation hazards. It is clear, however, that any radiation of gonads, and any substantial irradiation of other tissues, involve a chance of significant damage which requires assessment.

IV. General Recommendations Regarding the Medical and Occupational Irradiation of Human Beings

12. The Radiological Profession, through the International Commission on Radiological Protection,[3] has undertaken a valuable and responsible duty in defining maximum permissible limits of exposure for the main radiation hazards.

13. The establishment of these maximum permissible levels for those who are occupationally exposed to radiation depends on the view that there are doses which, in the light of our present knowledge, do not cause detectable somatic injury in the individual irradiated; and on the consideration that the number of individuals concerned is small enough for the genetic effects on the whole population to be negligible. For the gonads, or for irradiation of the whole body, the levels are such as to exclude doses greater than 0.3

[3] See the report of the International Commission on Radiological Protection, published in the *British Journal of Radiology*—Supplement 6, of December 1954, in the *Journal Francais d'electro-radiologie*—No. 10, of October 1955, etc.

rem in any week or 3.0 rem in any 13 weeks, or a sustained irradiation rate greater than 5 rem per year. These values imply that no total dose of over 50 rem will have been received by the gonads by the age of 30, or of over 200 rem by the whole body by the age of 60, in any occupationally exposed person.[4]

As regards irradiation of the whole population, it is considered prudent to limit the average dose to germinal tissues from artificial sources to the order of magnitude of that received from all natural sources.

14. In considering the extent to which the population is irradiated for medical purposes, it is essentially the genetic hazard which is involved although it seems possible that in certain circumstances somatic injury may occur occasionally after low doses of radiation arise. Otherwise, the relevant dose is that indicating the mean gonad irradiation among the population as a whole up to the end of the average reproductive period.

15. The extent of such genetic irradiation from diagnostic procedures has been found to be equal to at least 100% of all natural radiation in two countries,[5] and that from a third equalled at least 22% of this figure.[6] Even before obtaining more exact values for these and other countries, it is clear that the exposure can be substantial in countries with extensive medical facilities, and that it is essential to consider any ways in which this exposure could be reduced without detriment to the existing or developing value of medical radiology.

16. The Committee is therefore anxious to obtain the help of radiologists in suggesting through appropriate governmental channels any methods by which this total exposure could be reduced and in estimating the amount of reduction that might be expected from any such methods. In particular it would be valuable to know how much the radiation to the gonads could be reduced.

(a) by improved design or shielding of equipment,
(b) by fuller training of any individuals using radiographic or fluoroscopic equipment,
(c) by any local shielding of the gonads that is practicable, especially during abdominal or pelvic examination,
(d) by the use of technics involving radiography rather than fluoroscopy when full information can be obtained by this means,
(e) by improvement of administrative arrangements designed to obviate unnecessary repetition of identical examinations of the same subject,
(f) by a general study of certain medical conditions such as that of peptic ulcers, to identify the circumstances in which the establishment of a radiological diagnosis has or has not a definite influence upon the treatment or prognosis given.

[4] See the report of the International Commission on Radiological Protection, published in the *British Journal of Radiology*—Supplement 6, of December 1954, in the *Journal Francais d'electro-radiologie*—No. 10 of October 1955, etc.
[5] Sweden, United States of America.
[6] United Kingdom.

VI. Summary

1. The Scientific Committee on the Effects of Atomic Radiation established by the United Nations General Assembly accepts the view that the irradiation of human beings, and especially of their germinal tissue, has certain undesirable effects.

2. Information received so far indicates that, in certain countries (Sweden, United Kingdom, United States of America), by far the most important artificial source of such irradiation is the use of radiological methods of diagnosis and that this may be equal in importance to radiation from all natural sources. It is possible that such radiation may be having a significant genetic effect on the population as a whole.

3. The Committee is fully aware of the importance and value of the medical use of radiations but wishes to draw the attention of the medical profession to these facts and to the need for a more accurate estimate of the amount of exposure from this source. The help of the medical profession would be most valuable to make it possible to obtain fuller information on this subject.

4. The Committee would be particularly grateful for information through appropriate governmental channels on ways in which the medical irradiation of the population can be reduced without diminishing the true value of radiology in diagnosis or treatment.

REVIEWS

Electrocardiographic Test Book. Volumes I and II. Travis Winsor, Editor, with a review panel of 28 leading cardiologists. Volume I: 167 pages; Volume II: 132 pages; 22 × 28.5 cm. (paper-bound, loose-leaf). American Heart Association, Inc., New York. 1956. Price, $5.00.

This book has been sponsored by the Committee on Professional Education of the American Heart Association for the purpose of assisting students in the study of electrocardiography. In volume I are contained over 100 electrocardiograms with questions and an additional 237 questions on electrocardiographic interpretation, and an appendix. In volume II are contained the answers to these questions on electrocardiograms and electrocardiographic interpretations. The book was edited by Dr. Travis Winsor with the aid of a review panel with 28 leading cardiologists who acted as advisors and critics. The book is not meant to be a substitute for currently available texts on electrocardiography. It makes available a selective list of electrocardiograms which have been very well reproduced. There is often room for disagreement as to the interpretations of some of the electrocardiograms and the choice of the questions posed concerning some of the published records.

This book should be of value to medical students, house staff and practicing physicians as a collection of questions and answers on electrocardiography. In addition, the tables of normal values should be useful for reference purposes.

L. S.

Cardiac Emergencies and Heart Failure. By Arthur M. Master, M.D., Marvin Moser, M.D., and Harry L. Jaffe, M.D. 203 pages; 20.5 × 13.5 cm. Lea & Febiger, Philadelphia. 1955. Price, $3.75.

This is the second edition of this monograph which stresses prompt diagnosis in cardiovascular emergencies and their prompt treatment. Included in the present monograph are the newer therapies which have been developed since the earlier edition, three years previously.

This "pocket-size" text provides in readily accessible form practical information and advice on common cardiac conditions. There is an extensive bibliography which permits the more interested reader to explore further the recommendations of the authors. This text is of value to the practicing physician and student as a handy reference text.

L. S.

The Management of Tuberculosis: A Symposium. Edited by Irving J. Selikoff, M.D. 646 pages; 17.5 × 26 cm. Waverly Press, Inc., Baltimore, Maryland. 1956. Price, $5.00.

A symposium was prepared by members of the staff of the Mount Sinai Hospital of New York on the problem of the management of tuberculosis and published as the July-August 1956 issue of the *Journal of the Mount Sinai Hospital.* The present volume is a hard cover edition of that issue of the Journal.

With the rapid development of chemotherapeutic and surgical methods of treatment of tuberculosis in the past 10 years, and with the equally rapidly changing concepts of those doctors most concerned with the management of the disease, it is fortunate to have Dr. Selikoff and the staff of the Mount Sinai Hospital try their hand at summarizing our store of knowledge.

The section on antituberculous chemotherapy deals in a general way with the problems of chemotherapy, reviewing briefly its development, speculating as to the

mechanism of drug action, recording and commenting on pathologic observations in treated patients and then proceeding to an interesting discussion by Dr. Selikoff of the "limitations" of chemotherapy in tuberculosis. Under this heading he covers the toxicity of the individual drugs, the indications for their use, the problem of the morphology of the disease in relation to the prospect for cure with chemotherapy alone, and the problem of bacterial resistance. It is strangely interesting that the entire matter of human metabolism of isoniazid and the relationship of metabolic effect to therapeutic effect is not discussed. There is no significant analysis of the large scale controlled studies of the chemotherapy of tuberculosis carried out by the Veterans Administration, Army, Navy study group.

In the section on management, the principles of chemotherapy laid down are widely accepted and seem to be quite valid in the light of our present knowledge. The authors do, however, specifically endorse the use of all three drugs, SM-INH-PAS, in any but minimal disease. They suggest that no cavity should be designated as an example of open healing unless the sputum has been negative for tubercle bacilli by smear and by culture for at least one year. The approach to resectional surgery is conservative, and, very surprisingly, as much space is devoted to keeping pneumothorax and pneumoperitoneum alive as is given to decrying the widespread use of excisional surgery for the residual caseonecrotic focus. The surgical indications listed would represent the most minimal use of good thoracic surgical facilities and heavy reliance on long term chemotherapy alone in the management of pulmonary tuberculosis. Subsequently, however, in the section considering resectional therapy a detailed treatment of the rôle of surgery is given and the current status of surgical experience appraised.

Practically every phase of clinical tuberculosis is considered in the 19 papers that make up the book, including a concise treatment of the influence of tuberculosis on the function of the lung, a review of the problem of pleural effusion, consideration of tuberculosis of childhood, and discussion of tuberculosis of bone, kidney, intestine, skin, lymph nodes, and larynx.

The papers are well written, up to date, and collected together into one symposium represent, all in all, a fair statement of current opinion of the management of clinical tuberculosis.

PATRICK B. STOREY

New Bases of Electrocardiography. By DEMETRIO SODI-PALLARES, M.D., Chief of Department of Electrocardiography at National Institute of Cardiology of Mexico, Mexico City, with collaboration of ROYALL M. CALDER, M.D., editor, English translation, Clinical Professor of Medicine, Graduate School, Baylor University, Houston, Texas. 727 pages; 17.5 × 25.5 cm. C. V. Mosby Company, St. Louis. 1956. Price, $18.50.

This is the English edition of a book which has already seen three popular editions in Spanish. It is not a text devoted exclusively to clinical electrocardiography, but is one that is more specifically devoted to teaching and discussing the scientific bases of electrocardiography. This book also represents a summary of the research work done during the last eleven years in the Department of Electrocardiography of the Mexican Institute of Cardiology. The initial portion of the book is devoted to principles of electricity, electrophysiology, the electrical axis of the heart, unipolar limb leads, injured muscle, precordial leads, and the activation process of the human heart. Subsequent chapters concern themselves with the electrical and anatomical position of the heart, vectorcardiography, the ventricular gradient, and the intracavitary potential. In the appendix are included many of the details of mathematical and physical concepts which are referred to more briefly in the text. This book is

recommended as a text from which one can learn the basic concepts of electrophysiology. There is a good bibliography of 960 references, and the illustrations are numerous and clearly presented.

L. S.

Roentgen Signs in Clinical Diagnosis. By ISADORE MESCHAN, M.A., M.D., Professor and Director of the Department of Radiology at The Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina; Formerly Professor and Head of the Department of Radiology at the University of Arkansas School of Medicine, Little Rock, Arkansas; with the assistance of R. M. F. FARRER-MESCHAN, M.B., B.S., Melbourne, Australia. 1058 pages; 17 × 26 cm. W. B. Saunders Company, Philadelphia. 1956. Price, $20.00.

Roentgen Signs in Clinical Diagnosis is a new book in which not only the essentials, but also the pitfalls of correct roentgenologic interpretations are stressed. Roentgen diagnosis is stressed from a slightly different standpoint as the material has been organized, as far as possible, according to roentgenologic manifestations, rather than on an etiologic or anatomic basis, as in other texts. This method of organization seems quite useful in presenting the fundamental facts of roentgen diagnosis.

Illustrations are numerous, but a large number of these are only line sketches rather than actual roentgenographic reproductions. When accompanied by a roentgenogram, sketches are often useful for better illustration of certain points, but they should not replace roentgenograms, as in this book. It is often difficult, particularly for students, to transpose the pathologic findings from a sketch to an actual roentgenogram.

The bibliography has been intentionally limited, but it contains the main references on all the subjects.

This book is primarily a student text, illustrating basic points in roentgenologic interpretation and as such will prove valuable. It would not be particularly useful as a reference for radiologists and associated specialists.

J. M. D.

Clinical Examinations in Neurology. By Members of the Sections of Neurology and Section of Physiology, Mayo Clinic and Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, Rochester, Minnesota. 370 pages; 16 × 24.5 cm. W. B. Saunders Co., Philadelphia. 1956. Price, $7.50.

This volume is a presentation of the neurological examination and is written primarily for trainees in clinical neurology. It includes not only the technic of examination of the nervous system, but also the anatomy and physiology which form the background of the neurological examination. There has been a successful attempt to keep the book brief, as well as practical. The volume is of 369 pages, with 76 illustrations, mostly line drawings, 7 tables, and a good index. There are sections dealing with more specialized areas of the examination including neuro-ophthalmology, language, pain problems, electroencephalography, electromyography and spinal fluid. There is also one chapter on biochemical and pharmacologic aids in neurologic diagnosis.

This volume is essentially a handbook for the trainee in neurology at the Mayo Clinic, consequently there is much stress upon the recording of observations in the fashion developed at the Mayo Clinic. This particular aspect may at times appear unnecessarily ingenious to other readers who do not deal with the problems of a large group practice.

The book is of particular value to those in training but it will be of interest to anyone involved in clinical evaluation of neurological patients.

C. V. B.

Diagnosis and Treatment of Peripheral Vascular Disorders. By DAVID I. ABRAMSON, M.D., F.A.C.P., University of Illinois, College of Medicine. 537 pages; 17.5 × 26.5 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1956. Price, $13.50.

This is an extremely well organized guide to the diagnosis and treatment of peripheral vascular disorders. Because of its conciseness and inclusiveness, it should prove to be a valuable source of reference to the clinician.

Illustrations and charts are used to great advantage and add to the value of the contents. There are adequate and valuable references with each entity discussed. It is well indexed. An appendix includes the sources of proprietary drugs, instruments, etc. This again should be helpful to the clinician.

The material is organized into three parts: (1) differential diagnosis and signs and symptoms; (2) clinical entities and their treatment (this section contains many valuable and practical therapeutic suggestions); and, (3) a summary of the clinical anatomy and physiology of the peripheral circulation, clotting mechanisms and pharmacologic action of drugs.

G. H. Y.

Dermatology. By DONALD M. PILLSBURY, M.A., D.Sc. (Hon.), M.D., Professor and Director of Department of Dermatology, University of Pennsylvania School of Medicine; WALTER B. SHELLEY, M.D., Ph.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine; and ALBERT M. KLIGMAN, M.D., Ph.D., Associate Professor of Dermatology, University of Pennsylvania School of Medicine; 1331 pages; 17 × 25.5 cm. W. B. Saunders Company, Philadelphia. Price, $20.00.

This text by three of the country's foremost dermatologists presents an interesting departure from the formal style which is usually encountered in larger texts on dermatology. All of the authors are masters of lexicography, and this fact may be responsible for the easy-to-read "flowing style" in which the book has been written.

The ambiguous nomenclature associated with skin eruptions has presented an appalling problem to the American student of cutaneous medicine, and it is refreshing to note that in this text there is an attempt made to delete superfluous terms and to moderate some of the more lengthy and unwieldy names. The photographic reproductions are excellent.

The chapters dealing with physiology, anatomy, mycology and bacteriology of the skin present more than adequate information about these various subjects. They have been carefully written and contain the material essential for the graduate student in dermatology. The chapter on morphology of skin lesions is excellent. The descriptions of primary and secondary lesions are made more vivid by the inclusion of excellent photographs. Following the trend of modern teaching, the authors stress the relationship of cutaneous lesions to systemic disease.

Exceptions may be taken to the lack of adequate bibliographic references in a compendium of this size. It is a very detailed text more valuable to the graduate than to the undergraduate student. It well deserves a place in the library of every practicing dermatologist.

H. M. R., JR.

BOOKS RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Administrative Medicine: Transactions of the Fourth Conference, October 31, November 1, and 2, 1955, Princeton, N. J. Edited by GEORGE S. STEVENSON, M.D., National and International Consultant, National Association for Mental Health, New York, N. Y. 251 pages; 23.5 × 15.5 cm. 1956. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $4.25.

Atlas of Tumors of the Nervous System. By H. M. ZIMMERMAN, M.D., Chief, Laboratory Division, Montefiore Hospital, etc.; MARTIN G. NETSKY, M.D., Associate Neuropathologist and Associate Attending Physician in Neuropsychiatry, Montefiore Hospital, etc.; and LEO M. DAVIDOFF, M.D., Attending Neurological Surgeon, Montefiore Hospital, etc. 191 pages; 27.5 × 20 cm. 1956. Lea & Febiger, Philadelphia. Price, $25.00.

Carcinoma of the Breast: The Study and Treatment of the Patient. New England Journal of Medicine *Medical Progress Series.* By ANDREW G. JESSIMAN, F.R.C.S., M.D., Henry E. Warren Fellow and Assistant in Surgery, Harvard Medical School, etc.; and FRANCIS D. MOORE, M.D., Moseley Professor of Surgery, Harvard Medical School, etc. 135 pages; 19.5 × 12.5 cm. 1956. Little, Brown and Company, Boston. Price, $4.00.

Disease Control and International Travel: A Review of the International Sanitary Regulations. Special Number of the Chronicle of the World Health Organization (Vol. 10, No. 9–10). By H. S. GEAR, M.D., Assistant Director-General, Department of Central Technical Services; and Z. DEUTSCHMAN, International Quarantine Section. 71 pages; 24 × 18 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 70¢.

Diseases of the Heart and Circulation. 2nd Ed. By PAUL WOOD, O.B.E., M.D. (Melbourne), F.R.C.P. (London), Director, Institute of Cardiology, London, etc. 1,005 pages; 25 × 16 cm. 1956. J. B. Lippincott Company, Philadelphia. Price, $15.00.

The XIV. Japan Medical Congress. Parts I and II. Edited by the BUREAU OF ARCHIVES, The XIV. Japan Medical Congress at the Faculty of Medicine, Kyoto University. 733 pages (total, both volumes); 26 × 18 cm. (paper-bound). 1955. Publication supported by the Ministry Education Grant in aid for publicizing the results of scientific research.

Glaucoma: Transactions of the First Conference, December 5, 6, and 7, 1955, Princeton, N. J. Edited by FRANK W. NEWELL, M.D., Department of Surgery (Ophthalmology), The University of Chicago, Chicago, Ill. 251 pages; 23.5 × 15.5 cm. 1956. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $4.50.

The Head and Neck in Roentgen Diagnosis (in two volumes). 2nd Ed. By EUGENE P. PENDERGRASS, M.D., Professor of Radiology and Chairman of the Department of Radiology, University of Pennsylvania; J. PARSONS SCHAEFFER, M.D., Ph.D., Professor of Anatomy and Director of the Daniel Baugh Institute of Anatomy, Emeritus, Jefferson Medical College; and PHILIP J. HODES, M.D., Professor of

Radiology, University of Pennsylvania. 1,825 pages (total, both volumes); 26 × 18 cm. 1956. Charles C Thomas, Publisher, Springfield, Illinois. Price, $37.50.

Heart Sounds, Cardiac Pulsations, and Coronary Disease. Porter Lectures, Series 21. By WILLIAM DOCK, M.D., Professor of Medicine, State University of New York, College of Medicine at New York City. 98 pages; 21.5 × 14 cm. 1956. University of Kansas Press, Lawrence. Price, $2.50.

Klinische Physiologie und Pathologie. By PROF. DR. FERDINAND HOFF. 1,120 pages; 25 × 17.5 cm. 1956. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, $18.95.

Die Leberkrankheiten: Diagnostik und Therapie für die Praxis. By PROF. DR. KURT BECKMANN. 253 pages; 25 × 17.5 cm. 1957. Georg Thieme Verlag, Stuttgart; available in U. S. A. from Intercontinental Medical Book Corporation, New York. Price, $8.60.

Lymphatics, Lymph and Lymphoid Tissue. 2nd Ed. By JOSEPH MENDEL YOFFEY, D.Sc., M.D. (Manch.), F.R.C.S.(Eng.), Professor of Anatomy, University of Bristol; and FREDERICK COLIN COURTICE, M.A., D.Phil. (Oxon.), D.Sc. (Sydney), F.R.A.C.S. (Hon.), Director, Kanematsu Memorial Institute of Pathology, Sydney Hospital, Sydney. 510 pages; 24 × 15.5 cm. 1956. Published for The Commonwealth Fund by the Harvard University Press, Cambridge, Massachusetts. Price, $10.00.

The Patient Speaks: Mother Story Verbatim in Psychoanalysis of Allergic Illness. By HAROLD A. ABRAMSON, M.D., Associate Attending Physician and Chief of the Allergy Clinic, The Mount Sinai Hospital, New York City, etc. 239 pages; 21 × 13.5 cm. 1956. Vantage Press, New York. Price, $3.50.

The Philosophy of Medicine. By WILLIAM R. LAIRD, M.D. 64 pages; 22.5 × 14.5 cm. 1956. Education Foundation, Inc., Charleston, West Virginia. Price, $3.00.

Radiology of the Heart and Great Vessels. (A reprinting of Chapter IV from the 3-volume loose-leaf edition of *Golden: Diagnostic Roentgenology,* with the same page numbers used in that text.) By ROBERT N. COOLEY, M.D., Professor and Chairman of the Department of Radiology, University of Texas, Medical Branch, Galveston, Texas; and ROBERT D. SLOAN, M.D., Professor and Director of the Department of Radiology, University of Mississippi Medical Center, Jackson, Mississippi. 309 pages; 27.5 × 20 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, $12.00.

COLLEGE NEWS NOTES

Books Donated to the College Library of Publications by Members

The College gratefully acknowledges receipt of the following book from a Fellow of the College to the Memorial Library of the College:

Hans Popper, M.D., Ph.D., F.A.C.P., Chicago, Ill., *Liver: Structure and Function*, published by The Blakiston Division, McGraw-Hill Book Company, Inc., New York, Toronto, & London, 1957, 777 pages, illustrated; co-authored with Fenton Schaffner, M.D., F.A.C.P.

Foreign and International Meetings

Assembly of Association of French Speaking Doctors, Great Hall Faculty of Medicine, 85 Boulevard Saint-Germain, Paris, France, Oct. 16–18, 1957. For information address: General Secretary, Congrés Francais de Médecine, Prof. G. Boudin, Paris, France.

Canadian Medical Association, Edmonton, Alberta, Canada, June 17–21, 1957. Dr. A. D. Kelly, 150 St. George Street, Toronto 5, Ont., Canada, General Secretary.

Congress of International Society for Cell Biology, St. Andrews, Fife, Scotland, Aug. 28–Sept. 3, 1957. Prof. H. G. Callan, Bell Pettigrew Museum, The University, St. Andrews, Fife, Scotland, Secretary-General.

Congress of International Union Against Tuberculosis, New Delhi, India, Jan. 7–11, 1957. For information address: International Union Against Tuberculosis, 15 rue Pomerue, Paris 16e, France.

Inter-American Congress of Pan American Medical Association, Mexico City, Mexico, Nov. 18–22, 1957. Dr. Joseph J. Eller, 745 Fifth Ave., New York 22, N. Y., U. S. A., Executive Director.

Inter-American Medical Convention, Hotel El Panama, Panama City, Republic of Panama, April 3–5, 1957. Dr. William T. Bailey, Medical Association of the Isthmian Canal Zone, Box "E", Balboa Heights, Canal Zone, Chairman, Publicity Committee.

International Congress of Clinical Pathology, Brussels, Belgium, July 15–20, 1957. Prof. M. Welsch, Service de Bacteriologie et de Parasitologie, Universite de Liege, 32 Blvd., de la Constitution, Liege, Belgium, Secretary General.

International Congress of Dermatology, Stockholm, Sweden, July 31–Aug. 6, 1957. Dr. C. H. Floden, Karolinska, Sjukhuset, Hudkliniken, Stockholm 60, Sweden, Secretary General.

International Congress of Electroencephalography and Clinical Neurophysiology, Brussels, Belgium, July 21–28, 1957. For information address: Dr. R. G. Bickford, Mayo Clinic, Rochester, Minnesota, U. S. A.

International Congress of European Society of Haematology, Copenhagen, Denmark, Aug. 26–31, 1957. Dr. Aage Videbask, Blegdamsvej 11, Copenhagen, Denmark, Secretary General.

International Congress of International Society of Angiology, Mexico City, Mexico, Oct. 29–Nov. 2, 1957. Dr. H. Haimovici, 105 East 90th Street, New York 28, New York, U. S. A., Secretary General.

International Congress on Medicine and Surgery, Palazzo of Expositions at the Valentino, Turin, Italy, June 1–9, 1957. For information address: Segreteria Generale, Minerva Medica. Corso Bramante 83–85, Turin, Italy.

INTERNATIONAL CONGRESS OF MILITARY MEDICINE AND PHARMACY, Beograd and Opatija, Yugoslavia, Sept. 29–Oct. 5, 1957. Colonel Dr. Aleksandar Mezic, rue Nemanjina 15, Beograd, Yugoslavia, Secretary General.

INTERNATIONAL CONGRESS OF NEUROLOGICAL SCIENCES, Brussels, Belgium, July 21–28, 1957. For information address: Dr. Pearce Bailey, National Institute of Health, Bethesda 14, Maryland, U. S. A.

INTERNATIONAL CONGRESS OF NEUROPATHOLOGY, Brussels, Belgium, July 21–28, 1957. Dr. Ludo Jan Bogaert, 47 rue de l'Harmonic, Antwerp, Belgium, Secretary General.

INTERNATIONAL CONGRESS OF NUTRITION, Paris, France, July 24–29, 1957. For information address: Congress International de Nutrition, 71 Blvd. Pereire, Paris 17e, France.

INTERNATIONAL CONGRESS ON OCCUPATIONAL HEALTH, Helsinki, Finland, July 1–6, 1957. Dr. Pertti Sumari, c/o Tyoter Veyslaitos, Haattmaninkatu 1, Helsinki-Toolo, Finland, Secretary General.

INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES, Toronto, Ont., Canada, June 23–28, 1957. For information address: International Congress on Rheumatic Diseases, P. O. Box 237, Terminal "A," Toronto, Ont., Canada.

INTERNATIONAL GERONTOLOGICAL CONGRESS, Merano-Bolzano, Italy, July 14–19, 1957. For information address: Segreteria, Quarto Congresso Internazionale de Gerontologia, Viale Morgagni, 85, Firenze, Italy.

INTERNATIONAL NEUROLOGICAL CONGRESS, Brussels, Belgium, July 21–28, 1957. Dr. Ludo Jan Bogaert, Institut Bunge, 59 rue Philippe Milliot, Berchem, Antwerp, Belgium, Secretary General.

INTERNATIONAL SOCIETY FOR THE WELFARE OF CRIPPLES, London, England, July 22–27, 1957. For information address: Miss M. Drury, 34 Eccleston Square, London S. W. 1, England.

INTERNATIONAL SYMPOSIUM ON MEDICAL-SOCIAL ASPECTS OF SENILE NERVOUS DISEASES, Venice, Italy, July 20–21, 1957. For information address: Secretariate, Viale Morgagni 85, Firenze, Italy.

PAN AMERICAN CONGRESS ON CANCER CYTOLOGY, Miami Beach, Fla., U. S. A., April 25–29, 1957. Dr. J. Ernest Ayre, 1155 N.W. 14th St., Miami, Fla., U. S. A., General Chairman.

AMERICAN COLLEGE OF PHYSICIANS—REGIONAL MEETINGS

Territory	City	Date	Governor(s)	Official Guest(s)	Registration		
					Mbrs.	Non-Mbrs.	Total
I. Regional Meetings Concluded, Autumn 1956							
New England States & Provinces of Eastern Canada	Burlington, Vt.	Sept. 7–8	Elbridge E. Johnston	E. R. Loveland, Executive Secretary	58	51	109
North Dakota	Minot	Sept. 8	R. O. Goehl	Karver L. Puestow, Regent	21	19	40
West Virginia	Charleston	Sept. 29	P. H. Revercomb	Wallace M. Yater, Sec'y Gen'l	27	37	64
Hawaii	Honolulu	Oct. 10	Nils P. Larsen				30
New Mexico	Albuquerque	Oct. 16	R. Friedenberg	William B. Bean F. A. C. P.	21	39	60
Western New York	Albany	Oct. 19	John H. Talbott	Richard A. Kern, President-Elect			
Arkansas-Oklahoma	Tulsa, Okla.	Oct. 20	Bert F. Keltz John N. Compton	Philip S. Hench, Regent	59	43	102
Southeastern Regional Meeting (Ga., Fla., S. C., Ala., Cuba)	Nassau	Oct. 20–21	William C. Blake	E. R. Loveland, Executive Secretary Robert Wilson, Regent George F. Strong, Past President	73	97	170

AMERICAN COLLEGE OF PHYSICIANS—REGIONAL MEETINGS—*Continued*

Territory	City	Date	Governor(s)	Official Guest(s)	Registration		
					Mbrs.	Non-Mbrs.	Total
Puerto Rico	San Juan	Oct. 26–27	R. Rodriguez-Molina				
Midwest (Ill., Ind., Iowa, Minn., Wis.)	Minneapolis, Minn.	Oct. 27	Wesley W. Spink	Walter L. Palmer, President E. R. Loveland, Executive Secretary	172	114	286
New Jersey	Newark	Nov. 7	Edward C. Klein, Jr.	Walter L. Palmer, President E. R. Loveland, Executive Secretary	130	81	211
Montana-Wyoming	Great Falls, Mont.	Nov. 16–17	Harold W. Gregg	George H. Anderson, 3d Vice President	21	7	28
Pacific Northwest (Idaho, Ore., Wash., B. C.)	Portland, Ore.	Nov. 16–17	Merl L. Margason	Howard P. Lewis, Regent Fuller B. Bailey, Regent	82	19	101
Western Pennsylvania	Pittsburgh	Nov. 21	Frank J. Gregg				
Michigan	Ann Arbor	Dec. 1	H. Marvin Pollard	Chester M. Jones, 1st Vice President	132	108	240
North Carolina	Chapel Hill	Dec. 6	Elbert L. Persons	Walter L. Palmer, President	101	59	160
Kentucky-Tennessee	Nashville, Tenn.	Dec. 8	R. H. Kampmeier S. A. Overstreet	Walter L. Palmer, President	79	18	97

AMERICAN COLLEGE OF PHYSICIANS—REGIONAL MEETINGS—*Continued*

Territory	City	Date	Governor(s)	Official Guest(s)	Registration		
					Mbrs.	Non-Mbrs.	Total
II. Regional Meetings, Winter-Spring 1957							
District of Columbia—Maryland	Washington, D. C.	Jan. 12	John Minor R. C. Tilghman	Walter L. Palmer, President E. R. Loveland, Executive Secretary			
Ohio	Dayton	Jan. 17	Charles A. Doan	Walter L. Palmer, President			
Eastern Pennsylvania	Philadelphia	Jan. 18	Thomas M. McMillan	Walter L. Palmer, President Irving S. Wright, Gov. for N. Y.			
Colorado	Colorado Springs	Jan. 18–19	C. F. Kemper	Richard A. Kern, President-Elect			
Delaware	Wilmington	Feb. 9	L. C. McGee	Richard A. Kern, President-Elect E. R. Loveland, Executive Secretary			
Southern California	Santa Barbara	Feb. 23–24	George C. Griffith	Howard P. Lewis, Regent			
Nebraska	Omaha	Mar. 2	Edmond M. Walsh	Walter L. Palmer, President			
Virginia	Williamsburg	Mar. 2	Charles M. Caravati	Richard A. Kern, President-Elect E. R. Loveland, Executive Secretary			
Kansas	Topeka	Mar. 15	Wm. C. Menninger	Richard A. Kern, President-Elect			

Psychopharmacology Service Center

The Psychopharmacology Service Center has been established within the Research Grants and Fellowships Branch of the National Institute of Mental Health, Bethesda, Md.

The purpose of the Center is to implement a broad program of basic and clinical research aimed at increasing understanding of the mechanisms of action, efficacy, and limitations of the tranquilizing and other centrally active drugs. The program of the Center includes the stimulation and support of work on the basic pharmacological and psychologic mechanisms of drug action, experimental and clinical studies of drug effectiveness, and research aimed at the development of improved and new methods for predicting and evaluating the efficacy and toxicity of these compounds. The Center will perform informational, research advisory and coördinating functions, including consulting services, surveys, publication of a newsletter, summaries and reviews of recent and on-going research.

The professional staff of the Center at present consists of Jonathan O. Cole, M.D., Psychiatrist, as Chief, and Sherman Ross, Ph.D., as Research Psychologist. Other key professional personnel will include a Research Neuropharmacologist, a Research Statistician and a Research Scientist for information and editorial functions. Advisory panels consisting of leading scientific authorities representing the pertinent research areas will be appointed.

"The Medical Witness" Film

At the Clinical Meeting of the American Medical Association in Seattle, Wash., November, 1956, the first film, "The Medical Witness," of a series of educational films dealing with the professional relationships of doctors and lawyers was shown. It is now available for showings before medical societies, bar associations and other professional groups throughout the country. It is a 30-minute black and white 16 mm. film and depicts right and wrong methods of presenting medical testimony. The series of films is being produced by the William S. Merrell Company, Cincinnati. This film may be obtained on request to the Film Library, American Medical Association, 535 N. Dearborn St., Chicago 10, Ill.

Awards for Cerebral Palsy Research

Awards of more than $700,000.00 for a four-year investigation into the causes of cerebral palsy and mental retardation have been made to Yale University School of Medicine and to Brown University, according to a recent announcement by Doctor Leroy E. Burney, F.A.C.P., Surgeon General of the Public Health Service. These awards mark the beginning of a large coördinated research program which, during the next 10 to 20 years, will attempt to identify factors responsible for such disorders as cerebral palsy, mental retardation, blindness and deafness.

National Health Survey Program

Dr. Leroy E. Burney, F.A.C.P., Surgeon General of the Public Health Service, Department of Health, Education, and Welfare, announced a pilot test study which began on January 28 in Charlotte, North Carolina. The initial action will pre-test a number of aspects of a questionnaire being developed for national use at a later date. Interviewing will be conducted by the Bureau of the Census which is to perform this advance test and other field work on the national health survey for the Public Health Service. Data to be collected will include statistics on the number, age, sex, and occupation of persons suffering from diseases, injuries, or handicapping conditions; medical care received; the length of time that these people have been pre-

vented from carrying on their usual occupations or activities; and the economic and other impacts of such conditions. Information so collected will be kept confidential and only statistical totals will be published.

The National Health Survey is being undertaken under legislation requested by the Administration and enacted by Congress last summer. The new law authorizes the Surgeon General of the Public Health Service to make continuing annual surveys and special studies of the U. S. population to determine the extent of illness and disability and gather related information. The last previous such Federal survey was conducted 20 years ago.

Special Fellowship in Medical Neoplasia

Memorial Center for Cancer and Allied Diseases, New York City, is a training center affiliated with Cornell University Medical College. It participates actively in teaching at both undergraduate and graduate levels. It has a fully approved residency program in internal medicine, and, in addition, offers special fellowships for study to a limited number of graduate physicians.

The Memorial Center announces a special fellowship in medical neoplasia; annual stipend, $6,000, without maintenance. The fellowship appointment is for one year normally beginning July 1, renewable for one or two years for select individuals who develop a special interest in some problem.

The activities of the fellow include: clinical or clinical and laboratory study of an approved or assigned problem under reasonable guidance and supervision. The study is to be carried out at Memorial Center under the aegis of the Medical Neoplasia Service of the Department of Medicine. Available for clinical investigation are hospital records of 40 years, plus an active service consisting of approximately 40 beds in the Memorial Center, and two outpatient clinics in which an average of 70 patients are seen weekly.

Candidates must be graduates of approved medical schools, and must have completed or be in process of completing two years of postgraduate training in internal medicine in addition to one year of internship. Such training may be formal residency or its equivalent.

Candidates must be of the highest integrity and moral character and have an expressed interest, both academic and clinical, in the study of malignant neoplastic diseases.

Applications should be made in writing to Lloyd F. Craver, M.D., Chief, Medical Neoplasia Service, Memorial Center for Cancer and Allied Diseases, 444 E. 68th St., New York 21, N. Y.

American Academy of Pediatrics Spring Session

The American Academy of Pediatrics will hold its Spring Session at Washington, D. C., April 1–3, 1957, at the Sheraton-Park Hotel. Dr. Edgar P. Copeland, F.A.C.P., of Washington, will be the Honorary General Chairman, and will open the first general session. Among those of the College who will make presentations, and their subjects, are: Dr. Theodore Woodward, F.A.C.P., of Baltimore, Md., "Influence of Antibiotics on Immune Status"; Dr. Monroe Romansky, F.A.C.P., Washington, D. C., "Newer Antibiotics"; Dr. Sol Katz, F.A.C.P., Falls Church, Va., "Primary Tuberculosis."

Dr. Wallace M. Yater, F.A.C.P., Secretary General of the American College of Physicians, has been appointed as the representative of the American College of Physicians to the Committee on Medicine and the Health Professions, an outgrowth

of the White House Conference on a program for People-to-People Partnership. An objective is to encourage American citizens to develop their contacts with the peoples of other lands as a means of promoting understanding, peace, and progress. Dr. Louis H. Bauer, F.A.C.P., of New York, is Chairman.

The International Congress of Internal Medicine to Be Held in the United States, April 24–26, 1958

The International Congress of Internal Medicine for the first time will be held in the United States during the last three days of the week preceding the 39th Annual Session of the American College of Physicians in Atlantic City, April 28–May 2, 1958. Dr. T. Grier Miller, F.A.C.P., former President of the American College of Physicians, will be President of the Congress. Sir Russell Brain, F.A.C.P. (Hon.), President of the Royal College of Physicians of London, is President of the International Society of Internal Medicine. President Walter L. Palmer of the American College of Physicians has appointed the following coöperative committee to work with the International Congress: Dr. Wallace M. Yater, F.A.C.P., Washington, D. C., Chairman; Dr. Chester S. Keefer, F.A.C.P., Boston; and Mr. Edward R. Loveland, F.A.C.P. (Hon.), Philadelphia. The American committee appointed by the President of the Congress consists of, in addition to Dr. Miller, Dr. William S. Middleton, M.A.C.P., Washington, D. C., and Dr. Frank N. Allan, F.A.C.P., Boston. Additional members of the American committee may be added.

The Congress will make its headquarters at the new Sheraton Hotel in Philadelphia.

The Academy of Medicine of Cincinnati celebrated its 100th birthday at Cincinnati during the week of February 27–March 5, 1957. One hundred and seventy-five health and scientific exhibits, representing medicine, hospitals, research centers, public health, nursing, pharmacy, and industry were displayed in the spacious and historic Cincinnati Music Hall by the Cincinnati Health Museum. The American College of Physicians and other societies were among the exhibitors. Notable among the exhibits and occupying some 4,000 square feet of space was an Atomic Energy Exhibit from the American Museum of Atomic Energy entitled "Atoms for Peace." In the main foyer of the hall, "Juno," a full-sized, activated mannikin, graciously loaned for the occasion by the Dominican Republic, was on display. Dr. Paul D. White, M.A.C.P., and Dr. Walter Alvarez, F.A.C.P., noted medical scientists and authors, were among the distinguished guest speakers. The Centennial Convocation address was given by Sir Edward Appleton, Nobel Laureate, Edinburgh, Scotland. Professor Reginald McGrane, Chairman of the Department of History, University of Cincinnati, prepared a one hundred year history of the Academy of Medicine, entitled "The Doctor's Forum."

Fellowship in Cardiology Available, San Francisco Veterans Administration Hospital

A fellowship in cardiology has been made available at the Veterans Administration Hospital, San Francisco, Calif., as of July 1, 1957. The fellowship will be supported by the San Mateo County Heart Association, the fellow being appointed from Stanford University School of Medicine. The stipend will be $3,600 per annum. Appointments are renewable. Applicants must be graduates of a Class A medical school and citizens of the United States.

Several fellowships are also available in Hematology and Chemotherapy of Tumor and Lymphoma, in conjunction with Stanford University School of Medicine. These

fellowships are supported by the National Institutes of Health in conjuction with a research program.

Future Meetings, American Public Health Association

The Executive Board of the American Public Health Association announces the following dates for the 85th and 86th Annual Meetings: November 11–15, 1957, Cleveland, Ohio; October 27–31, 1958, St. Louis, Mo.

Preventive Medicine Residency Program Established by Army Medical Service

The Army's first formal residency training program in preventive medicine will begin July 1, 1957, according to an announcement by the Army Surgeon General's Office in Washington. Establishment of this new program is in keeping with the Army's intended leadership in the field of preventive medicine. Regular Army Medical Corps officers or qualified civilian physicians who accept commissions in the Regular Army are eligible to participate in this program. Interested civilian physicians may apply to The Surgeon General, Department of the Army, Washington 25, D. C., Attention: Chief, Personnel Division. Military personnel should apply through appropriate channels.

The residency is a three-year program providing both civilian and military training. The first year of training will be an eleven-month course in military preventive medicine at Walter Reed Army Institute of Research in Washington, or an equivalent graduate course in preventive medicine or public health at a civilian university. The second year will be spent in an approved civilian residency training program in a city, county, district, or state health department. The third year will consist of formal military residency training at a large Army post with a small portion of the time at a nearby Army headquarters under the supervision of the preventive medicine officers. The military phase of residency training may be omitted for certain individuals with previous military experience.

Postgraduate American Assembly in Fertility and Sterility

The New York Medical College-Metropolitan Medical Center has announced the First American Postgraduate Assembly in Fertility and Sterility, to be held in New York City at the College and affiliated hospitals from May 18–31, 1957. Emphasis in the course will be placed on the clinical aspects of human infertility including recent advances in diagnosis and therapy. A unique feature will be special sessions devoted to methods and problems in the organization and administration of sterility clinics, services, and teaching programs. The program will consist of lectures, demonstrations, round-tables, operative clinics including culdoscopy and tubal surgery, ward rounds and specialty-clinic case presentations. The course has been scheduled for the end of May, 1957, so as to allow the registrants the opportunity to attend the annual scientific meetings of the American Society for the Study of Sterility, The Endocrine Society, and the American Medical Association, which will be held in New York City starting May 31, 1957.

Information and applications may be obtained from Dr. Ralph E. Snyder, Dean, New York Medical College, 1249 Fifth Ave., New York 29, N. Y. Tuition, $150.00.

The Twenty-Sixth Annual Spring Clinical Conference of the Dallas Southern Clinical Society was held at Dallas, March 18–20, 1957. Among the guest speakers were Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia (Radiology); Dr. Tinsley

R. Harrison, F.A.C.P., Birmingham (Internal Medicine); and Dr. Wesley W. Spink, F.A.C.P., Minneapolis (Internal Medicine).

The National Jewish Hospital, Denver, Colo., a free, non-sectarian institution, is expanding its facilities for cardiovascular patients with lesions amenable to surgical intervention. Only patients unable to pay for private care are eligible for admission. Since the hospital has a complete cardio-pulmonary physiology laboratory, definitive diagnosis by the referring physician is not necessary. The program is under the direction of Dr. Irving Kass, (Associate), and Dr. Abe Ravin, F.A.C.P.

Cardiac Arrhythmias, University of Kansas Medical Center

Cardiac Arrhythmias was the subject of a two-day postgraduate course on The Heart, presented on February 25–26, at the University of Kansas Medical Center, Kansas City, Kans. Much of the teaching was accomplished through demonstration of cases presenting arrhythmias. The guest faculty included, among others, Dr. Samuel Bellet, F.A.C.P., Philadelphia, Dr. Calvin F. Kay, F.A.C.P., Philadelphia, and Dr. R. Bruce Logue, F.A.C.P., Atlanta.

Golden Anniversary Celebrated by Southern Medical Association

The Southern Medical Association celebrated its Golden Anniversary, fifty years of service to physicians of the South, at Chattanooga, Tenn., last Oct. 2–3, 1956. The first meeting of the Association was held at Chattanooga, Oct. 2–3, 1906, and a considerable number of the original group, still living, were among those in attendance at the Golden Anniversary.

The American Society of Internal Medicine, formally organized during the 37th Annual Session of the American College of Physicians at Los Angeles, will hold its first Annual Meeting at Boston, Mass., April 7, 1957, the day preceding the opening of the 38th Annual Session of the College. Meetings of the Society will be held at the Hotel Statler.

Dr. Michael M. Dacso, (Associate), Director of the Department of Physical Medicine and Rehabilitation at Goldwater Memorial Hospital, New York, and Associate Professor of Clinical Physical Medicine and Rehabilitation at New York University College of Medicine, was recently appointed Special Consultant, United States Public Health Service, Bureau of State Services, Division of Special Health Services, Chronic Disease Branch.

The 35th annual scientific and clinical session of the American Congress of Physical Medicine and Rehabilitation will be held Sept. 8–13, 1957, at Hotel Statler, Los Angeles, Calif.

Dr. Thomas M. Rivers of New York City is now Medical Director of the National Foundation for Infantile Paralysis. He succeeds Dr. Hart E. Van Riper, who resigned to accept the Medical Directorship of Geigy Pharmaceuticals, New York.

Dr. George P. Heffner, F.A.C.P., Charleston, W. Va., has been reëlected Governor for West Virginia of the American Diabetes Association.

Dr. Reverdy H. Jones, Jr., F.A.C.P., Roanoke, Va., has been elected a Vice President of the Medical Society of Virginia. Dr. Walter P. Adams, F.A.C.P., Norfolk, was elected a Councilor, as was also Dr. David W. Scott, Jr., F.A.C.P., Fredericksburg.

Dr. Turner Z. Cason, F.A.C.P., Jacksonville, Fla., is President of the Duval District Heart Association.

Dr. J. E. Acker, Jr., (Associate), Knoxville, Tenn., is President, and Dr. B. M. Overholt, F.A.C.P., Knoxville, is President-Elect of the East Tennessee Heart Association.

Dr. Lynwood D. Zinn, F.A.C.P., Clarksburg, W. Va., is Vice President of the West Virginia Heart Association.

Dr. Louis A. M. Krause, F.A.C.P., was the guest speaker at the Golden Anniversary of the Eastern Panhandle Medical Society at Martinsburg, W. Va., December 1, 1956.

Dr. Jack Masur, F.A.C.P., Washington, D. C., has been assigned by the Surgeon General of the Public Health Service as Director of the Clinical Center at the National Institutes of Health in Bethesda, Md.

The Michigan Pathological Society has established the Carl V. Weller Lectureship in recognition of the contributions made by Dr. Weller, F.A.C.P., in the fields of pathology and clinical pathology. Dr. Howard T. Karsner, F.A.C.P., Washington, D. C., Medical Advisor to the Navy, delivered the first Weller Lecture at Ann Arbor on December 8, 1956.

Dr. Francis J. Braceland, F.A.C.P., President of the American Psychiatric Association, delivered the first annual lecture of the Robert S. Johnson, Jr., Memorial Lectures at the Boston State Hospital during the past Autumn.

Dr. Paul D. White, M.A.C.P., Boston, and Dr. Edwin C. Andrus, F.A.C.P., Baltimore, were guest speakers on the New York Heart Association's recent conference on "Atherosclerosis and Coronary Heart Disease."

Dr. Aaron E. Margulis, F.A.C.P., Santa Fe, N. M., has been appointed by the New Mexico Medical Society as its state scientific editor and member of the Rocky Mountain Medical Journal editorial board. Dr. Margulis succeeds Dr. Carl H. Gellenthien, F.A.C.P., Valmora, who had served almost twelve years.

1957 Officers, Joint Commission on Accreditation of Hospitals

The following officers of the Joint Commission on Accreditation of Hospitals have been elected for the year 1957:

Julian P. Price, M.D.—Chairman
Alexander M. Burgess, M.D., F.A.C.P.—Vice Chairman
Mr. Stuart K. Hummel—Treasurer
Kenneth B. Babcock, M.D.—Secretary

Dr. Samuel Morrison, F.A.C.P., Associate Professor of Medicine and Associate Professor of Gastro-enterology at the University of Maryland School of Medicine, has recently been appointed Chief of Medical Service at St. Joseph's Hospital, Baltimore, Md.

Dr. Lowell T. Coggeshall, F.A.C.P., resumed his duties January 1, 1957, as Dean of the Division of Biological Sciences at The University of Chicago following his resignation, effective December 28, 1956, as Special Assistant to Secretary Folsom of the Department of Health, Education and Welfare. Dr. Coggeshall received the commendation of President Eisenhower for the progress made in the health field during the last year and for his outstanding performance.

Dr. Coggeshall is President-Elect of both the American Cancer Society and the Association of American Medical Colleges.

At the 53rd Annual Congress on Medical Education and Licensure, held in Chicago, February 9–12, 1957, the following Fellows of the College participated on the program: E. Hugh Luckey (New York City), William B. Bean (Iowa City), Dana W. Atchley (New York City), W. Barry Wood (Baltimore), William A. Sodeman (Columbia, Mo.), Mahlon H. Delp (Kansas City, Kans.), Charles F. Wilkinson, Jr. (New York City), Willard C. Rappleye (New York City), and S. M. Poindexter (Boise).

Dr. Marion A. Blankenhorn, F.A.C.P., Cincinnati, officially represented the American College of Physicians at the Centennial Celebration of the Cincinnati Academy of Medicine in February, 1957.

The Second Inter-American Medical Convention will convene at the Hotel El Panama, Panama City, Republic of Panama, April 3–5, 1957, under the sponsorship of the Medical Society of the Isthmian Canal Zone, a chapter of the American Medical Association since 1906. Colonel Charles O. Bruce, MC, USA, Chief Health Officer of the Panama Canal Company and President of the Medical Society, will act as keynote speaker at the invocation ceremonies, which will include also addresses by the President of the Republic of Panama and by the Governor of the Panama Canal Zone.

In addition to the scientific program, a full round of entertainment is planned for families who accompany the delegates.

Dr. Howard P. Lewis, F.A.C.P., Professor of Medicine at the University of Oregon Medical School, acted as the 1956 Physician-in-Chief Pro Tempore to the Cleveland Clinic Foundation. Dr. Lewis spent three days, December 13–15, 1956, with the resident staff in internal medicine at the Cleveland Clinic and the Cleveland Clinic Hospital, and presented a paper to the entire staff on the morning of December 15, "A Rare but Interesting Condition—Pseudoxanthoma Elasticum and Arterial Disease."

The 26th Venereal Disease Postgraduate Conference for physicians sponsored by the University of Tennessee College of Medicine and the Public Health Service will be held at Memphis, April 18–20, 1957. The course is designed to acquaint the

practitioner with the latest developments in diagnosis, treatment and management of venereal diseases. No tuition will be charged. Applications for admission may be sent to Dr. Henry Packer, F.A.C.P., Department of Preventive Medicine, University of Tennessee College of Medicine, Memphis 3, Tenn.

Dr. Leo H. Criep, F.A.C.P., Associate Professor of Medicine, University of Pittsburgh School of Medicine, delivered a lecture on "Hypersensitiveness—Relation to Collagen Diseases," January 3, 1957, before the University of Miami School of Medicine, Miami, Fla.

Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala., was unanimously elected President-Elect of the Interstate Postgraduate Medical Association of North America at its last annual meeting in Cleveland, Ohio. Dr. Spies is Scientific Director of the Nutrition Clinic, Hillman Hospital, Birmingham, and Professor and Head of the Department of Nutrition and Metabolism, Northwestern University Medical School, Chicago, Ill.

Dr. I. H. Richter, F.A.C.P., has been appointed Attending Physician in Peripheral Vascular Diseases at the Brooklyn Women's Hospital, Brooklyn, N. Y.

Dr. George W. Dana, (Associate), Assistant Professor in Medicine at Tufts University Medical School, Medical Staff Director of the New England Center Hospital, and Medical Director of the Bingham Associates Fund, Boston, was the Chairman of a Regional Postgraduate Medical Clinic on "Influence of Emotional Factors on Certain Diseases" at Boston, January 14, 1957. Dr. Franz J. Ingelfinger, F.A.C.P., covered the subject as it applies to Gastroenterology, Dr. Robert P. McCombs, F.A.C.P., for the field of Asthma, Dr. James F. Patterson, (Associate), Dermatology, and Dr. Louis A. Selverstone, (Associate), Cardiology. Other speakers covered the subject as it applies to Arthritis and Rheumatic Diseases, Rheumatism, and Medical Gynecology.

The Fourth International Poliomyelitis Conference will be held in Geneva, Switzerland, July 8–12, 1957, under the patronage of the President of the Swiss Confederation. Governments are invited to send official delegates to participate in the Conference. These invitations are being extended by the Federal Political Department of the Swiss Government through its Embassies and Legations. Invitations are also sent to various universities and scientific institutions, to members of scientific and philanthropic societies, and directly to doctors and scientists. For copies of the program and other information contact Fourth International Poliomyelitis Conference, Secretariat, Hotel du Rhone, Geneva, Switzerland. Travel arrangements are set up with Thos. Cook & Son and the American Express Company.

Dr. George W. Thorn, F.A.C.P., will be the Taub Visiting Professor of Internal Medicine for 1956–57 at Baylor University College of Medicine. Dr. Thorn is the Hersey Professor of Theory and Practice of Physic at Harvard Medical School and Physician-in-Chief of Peter Bent Brigham Hospital.

Dr. Thorn conducted daily teaching conferences at the Jefferson Davis, Veterans Administration, and Methodist Hospitals and Baylor University College of Medicine, February 4–8, 1957.

Veterans Administration, Clinical Investigator Program

Announcement has been made that the Veterans Administration Medical Program plans to train selected physicians and dentists whose primary responsibility will be medical research. The candidates must be interested in problems of particular importance in the care of veteran patients in the fields basic to neurology and psychiatry, cardiovascular disease, cancer, degenerative diseases, and problems involving the aging process. Maximum freedom of choice of subject will be allowed within these broad fields.

Any physician or dentist will be eligible who has completed at least the formal residency training period required prior to American Specialty Board certification and who has special interest and aptitude to do full-time research for a period of possibly up to three years. Beginning salary will be $8,990.00 per annum, with some additional credit for certification.

A Central Advisory Committee composed of outstanding educators and investigators will make the selections. The candidate should submit a curriculum vitae, including transcripts of his scholastic record and any other information helpful to the Committee in its evaluation. He should prepare a detailed description of his proposed research program and make a brief statement of his future plans and ambitions. The candidate should select a preceptor who will follow his career throughout the period of appointment. The preceptor may be any person approved by the Deans Committee, within or without the Veterans Administration. Selections will be made semi-annually for January and July appointment. Applications may be obtained from the manager of the Veterans Administration hospital of choice. The completed forms will be submitted by the Deans Committee to the Office of the Assistant Chief Medical Director for Research and Education, Veterans Administration, Washington 25, D. C.

Graduate Fellowships in Industrial Medicine

The University of Cincinnati's Institute of Industrial Health is offering graduate fellowships in Industrial Medicine, providing professional training for graduates of approved medical schools who have completed at least one year of internship.

The three-year course of instruction, leading to the degree of Doctor of Science in Industrial Medicine, satisfies admission requirements for certification in Occupational Medicine by the American Board of Preventive Medicine. Stipends vary from $3,000.00 to $4,000.00 per annum, according to dependents. Further information may be obtained from the Secretary, Institute of Industrial Health, University of Cincinnati College of Medicine, Cincinnati 19, Ohio.

Research into the Cure and Treatment of Rheumatic Fever

A $600,000.00 fund for research into the cure and treatment of rheumatic fever and related diseases has been established at the Northwestern University Medical School, Chicago, by Samuel Sackett of Evanston, Ill. It is probably the largest single gift ever made by an individual for rheumatic fever study, according to Dr. J. Roscoe Miller, F.A.C.P., President of Northwestern University.

Dr. Gene H. Stollerman, F.A.C.P., Assistant Professor of Medicine at Northwestern, will direct the program.

Cancer Research, National Cancer Institute of The Public Health Service

A research training program to increase scientific manpower for clinical and non-clinical cancer research has been established by the National Cancer Institute of the Public Health Service, Department of Health, Education and Welfare. Funds totaling $1,200,000.00 were appropriated for the program by Congress. Surgeon General Leroy E. Burney has approved fifteen research training grants to fourteen institutions whose applications were recommended by the National Advisory Cancer Council. Slightly more than half of the total appropriation has been earmarked by Congress especially for training in the fields of chemotherapy and steroid hormones.

Among institutions to which grants have been made for this research are: University of Utah, Clark University, Columbia University, Yale University, Sloan-Kettering Institute for Cancer Research, Roswell Park Memorial Institute, University of Wisconsin, University of Minnesota, University of Kansas, Brown University, Stanford University, Washington University, Roscoe B. Jackson Memorial Laboratory and Massachusetts General Hospital.

Information concerning this program may be obtained through the Research Grants and Fellowships Branch, National Cancer Institute, Bethesda 14, Md.

Francis D. Murphy Chair of Medicine Endowed

Rev. Edward J. O'Donnell, S. J., president of Marquette University, and Dr. John S. Hirschboeck, M.D., F.A.C.P., dean of the medical school, have announced the creation of an endowed chair of medicine, to be called "The Francis D. Murphy Chair of Medicine." The endowment of $350,000, established anonymously by a Milwaukee donor, will honor Francis D. Murphy, M.D., F.A.C.P., the present professor and director of the department of medicine, for 35 years of service devoted to the school. The income and principal of this endowment is to be spent over a period of 25 years and will presently pay the salaries of two full-time associate professors. Upon Dr. Murphy's retirement, the full-time professor and director of the department of medicine will receive his appointment through this endowment as the Francis D. Murphy professor of medicine.

Dr. Murphy has been on the faculty of medicine since 1922. In 1923 he became Medical Director of the Milwaukee County Hospital, a position he still serves. He has been active in academic circles, has done much writing and research, and is a well known speaker at national meetings. He has been a Fellow of the American College of Physicians since 1928. In 1952 the Marquette Medical Alumni Association presented him with the medical alumnus award of the year. In 1956 he received the Marquette University Alumnus of the Year Award.

OBITUARIES

RECENT DEATHS OF A.C.P. MEMBERS

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

Dr. Edward John Gillespie Beardsley, F.A.C.P., Philadelphia, Pa., Dec. 27, 1956
Dr. Charles Palmer Bondurant, F.A.C.P., Oklahoma City, Okla., Oct. 23, 1956
Dr. Douglas Boyd, F.A.C.P., Highland Park, Ill., date unknown
Dr. Robert Emmett Britt, F.A.C.P., St. Louis, Mo., Oct. 28, 1956
Dr. John Molloy Flynn, F.A.C.P., Boston, Mass., Dec. 11, 1956
Dr. Roy Luther Langdon, F.A.C.P., Philadelphia, Pa., Dec. 21, 1956
Dr. Walter Bradford Metcalf, F.A.C.P., Los Altos, Calif., Sept. 2, 1956
Dr. Samuel Archer Munford, F.A.C.P., Clifton Springs, N. Y., Oct. 29, 1956
Dr. Harry Evans Patrick, F.A.C.P., Youngstown, Ohio, Sept. 28, 1956

The College headquarters at 4200 Pine St., Philadelphia 4, Pa., would appreciate it if members and readers send in notices of the deaths of members promptly, so that suitable obituaries may be prepared and published. Frequently, deaths of members are not reported for several weeks or even months after a member is deceased.

DR. STEPHEN HORACE CURTIS

Stephen Horace Curtis, M.D., Troy, N. Y. Born, May 30, 1894; M.D., 1915, Union University, Albany Medical College; postgraduate training included work in pathology and bacteriology at the Bender Hygienic Laboratory, Albany, and the Rockefeller Institute of Medical Research, New York City, 1916–17; attended the U. S. Army Medical School, Washington, D. C., 1917–18, and served in the U. S. Army, A.E.F. in 1918–20; Instructor in pathology and bacteriology, 1916–17, Albany Medical College; Instructor in Medicine, 1920–25, Albany Medical College; Instructor in Bacteriology, 1920, U. S. Army Medical School; Intern, 1915–16, Samaritan Hospital, Troy; Resident in Pathology, 1916–17, Albany Hospital; Associate in Medicine, 1920–25, Samaritan Hospital, Troy; Director of Laboratories, 1920–35, Leonard Hospital, Troy; Metabolist, 1925–35, Leonard Hospital, Troy; Diplomate, American Board of Pathology; Fellow of the American College of Physicians since 1936; member of the House of Delegates, New York State Medical Association for several years; member, American Medical Association, American Society of Clinical Pathologists, Radiological Society of North America, American Public Health Association, American Association for the Study of Neoplastic Diseases, Pan-American Medical Association; author of a number of papers in leading medical journals.

Dr. Curtis became associated with the College as an Associate in 1933 and was advanced to Fellowship in 1936. He was regular in his attendance at the annual sessions and always an interested member of the College, a beloved physician and a fine gentleman. Death was caused by coronary occlusion. Surviving Dr. Curtis is his widow, Mrs. Frances M. Curtis (Cedar Hedges, Troy, N. Y.).

JOHN H. TALBOTT, M.D., F.A.C.P.,
Governor for Western New York

DR JOHN SEVERY HIBBEN

After a long, disabling illness, Dr. John Severy Hibben, F.A.C.P., who practiced in Pasadena since 1916, succumbed to successive cerebral thromboemboli on

Sept. 30, 1956, at the age of 68. Dr. Hibben, who was born on Sept. 10, 1888, in Topeka, Kans., attended Stanford University and received his M.D. degree from the University of Southern California School of Medicine in 1914. Interested primarily in physical medicine, Dr. Hibben was on the Editorial Board of the *Archives of Physical Medicine* from 1930 through 1937, presided over the American Congress of Physical Medicine in 1935, and was for many years Chairman of the Committee on Physical Medicine and a member of the Senior Staff at the Collis P. and Howard Huntington Memorial Hospital. He was also on the Senior Staff of St. Luke Hospital.

Dr. Hibben served as President of the Pasadena-Alhambra branch of the Los Angeles County Medical Association in 1945, and as Chairman of the Board of Governors of that body in 1946–1948. He was a member of the American Congress of Physical Medicine; Pacific Physical Medicine Association; California State Medical Association; Founder and past Chairman of a special committee on Physical Medicine, 1932–36, California State Medical Association; Staff Physician, 1937–41, Pasadena Community Playhouse; member, Los Angeles County Medical Society; American Medical Association; Pasadena Medical Society; Los Angeles Society of Internal Medicine; Diplomate, American Board of Physical Medicine; and in 1949 elected to Fellowship in the American College of Physicians. Dr. Hibben was the author of a host of published papers.

Dr. Hibben is survived by his wife, Mrs. Jess W. Hibben, of 547 E. California St., Pasadena.

GEORGE C. GRIFFITH, M.D., F.A.C.P.,
Governor for Southern California

DR. SIDNEY LECHNER

Dr. Sidney Lechner died on October 23, 1956, in New York City, of an acute myocardial infarction with thrombus in the left ventricle which resulted in multiple emboli to the mesenteric, splenic, hepatic and femoral arteries. A contributory cause of death was peripheral vascular disease.

Dr. Lechner was born on March 13, 1906, New York City. He received his degree of Doctor of Medicine at University of Maryland School of Medicine in 1932. He interned at Jewish Memorial Hospital, New York City. He did postgraduate work in Cardiology and Gastroenterology (1946–1947) at Montefiore Hospital, New York City, and also postgraduate work in Peripheral Vascular Disease, Ophthalmology, Pathology and Psychiatry (1948–1949) at Mt. Sinai Hospital, New York.

His hospital appointments were as follows: He was Adjunct in Gastroenterology (since 1938) at Jewish Memorial Hospital; and Associate Attending Physician at Fordham Hospital (since 1952).

He was a diplomate of the American Board of Internal Medicine and was a member of the Bronx County Medical Society, New York State Medical Association, American Medical Association, National Gastroenterological Association and American Heart Association. He had been an Associate of the American College of Physicians since 1953. His practice was restricted to Internal Medicine and Gastroenterology.

Dr. Lechner is survived by his widow, Mrs. Sidney Lechner, 240 St. Johns Avenue, Yonkers, New York, and one son who is a senior pre-medical student at New York University. His confreres note with sincere regret the passing of Dr. Lechner.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor, Eastern New York State

DR. GEORGE MAX LEVITAS

Dr. George M. Levitas who, for almost fifty years, ministered to the sick of Bergen County, N. J., died September 16, 1956, in his home at Westwood.

A native of Estonia, Dr. Levitas came to the United States at the age of nine and moved to Westwood in 1906 after receiving his medical degree from the Long Island College Hospital in 1904. He also attended Cornell University. He practiced pediatrics and general medicine until 1950 when he retired. In his early days of practice Dr. Levitas used a bicycle for transportation when calling on patients.

Dr. Levitas was associated with Hackensack Hospital and retired as Chief of Pediatrics there in 1946. The Bergen County Tuberculosis and Health Association in which he was active for many years credits him with establishing the first cardiac clinic at Hackensack Hospital, in 1940. He was also a member of the Board of Governors of Bergen Pines Hospital and physician of the Bergen County Home for the Indigent, both in Paramus.

A past president of the Bergen County Medical Society, he was also a Fellow of the American College of Physicians and a member of the American Geriatrics Society. He was the first president of the local chapter of the American Red Cross in 1917 and served as a medical examiner for Selective Service boards during World Wars I and II. He also had been a fire department surgeon during his long career.

The local Rotary Club listed him as its first president and the Bergen County Y.M.H.A. as a former president. Other organizations to which he belonged were the Hackensack Elks Lodge 658, Royal Arcanum of Westwood, Odd Fellows of Westwood, Fulton Lodge, F. and A. M., Salaam Shrine Temple, Craftsmen's Club, Grand Street Boys Association of New York City, Lions Club, Hackensack Golf Club, and Mountain Ridge Country Club.

Surviving him are his wife, the former Lillian Israel, two sons, Dr. Irving M. Levitas, F.A.C.P., and Guilford Levitas, D.D.S., both of Westwood; also a daughter, Mrs. Gladys Cooper of Tenafly.

IRVING M. LEVITAS, M.D., F.A.C.P.

DR. JOHN WILLIAM SHUMAN, SR.

Dr. John William Shuman, Sr., F.A.C.P., of Santa Monica, died on August 4, 1956, at the age of 71 of carcinoma of the bladder. Dr. Shuman, who was born in Washington, Iowa, in 1885, received his M.D. degree from the University of Pittsburgh School of Medicine in 1910, and served his country in both world wars—as Major in World War I, and as Lieutenant Colonel in World War II.

Having practiced in the Southern California area since 1924, Dr. Shuman was on the staff of the Hollywood-Presbyterian Hospital for many years. He gave up private practice just prior to World War II and, following release from service, accepted a post as internist with the Domiciliary Medical Unit, Veterans Administration Center at Los Angeles. A Diplomate of the American Board of Internal Medicine, Dr. Shuman was Senior Attending Physician, Emeritus, at the Los Angeles County Hospital at the time of his retirement from active practice in 1953. Dr. Shuman was a prolific writer, having published over two hundred articles in leading medical journals.

He was a member of the American Medical Association; Los Angeles County Medical Association; California State Medical Association; American Association of Military Surgeons; Hollywood Academy of Medicine, President (1936); Honorary Member, American Geriatrics Society; elected to Fellowship (1919), American College of Physicians.

Dr. Shuman is survived by his widow, Mrs. Adeline D. Shuman of 507 Eleventh St., Santa Monica; a daughter, Mrs. R. E. Britton of Los Angeles; a son, Richard D. Shuman of Washington, D. C.; a sister, Mrs. Jean Smith of Keene, Calif., and twelve grandchildren.

GEORGE C. GRIFFITH, M.D., F.A.C.P.,
Governor for Southern California

DR. CHARLES WILLIAM WARREN

Dr. Charles William Warren was born in Clyde, N. Y., August 15, 1900. He graduated from Syracuse University College of Medicine in 1924. Following an internship in St. Agnes Hospital in Baltimore, Md., 1924–25, he was an intern and resident at Clifton Springs Sanitorium, N. Y., 1925–28. For many years he was a staff member of the Rochester General Hospital, the Strong Memorial Hospital and the Genesee Hospital. He was a member of the faculty of the University of Rochester School of Medicine since 1930, and served as Assistant Physician in the outpatient department and the diabetes and allergy clinics. He was a Diplomate of the National Board of Medical Examiners and the American Board of Internal Medicine, and a member of the American Academy of Allergy, the American Medical Association, and the American Diabetes Association. He was elected a Fellow of the American College of Physicians in 1934.

Dr. Warren was well known and genuinely liked by the Rochester community physicians. He was beloved by his patients. His calm and easy manner inspired their confidence. His sincere interests in their complaints made him highly effective in dealing with their problems. He was especially gifted in the management of the chronically ill and the aged. His colleagues knew him to be methodical, conscientious, meticulous in his personal habits and in his practice. He could not compromise with himself and he worked late hours and spent much time with each of his patients. He never refused the late night call even when his own cardiac status seemed to be precarious. If one word were adequate to describe Charles, it might be "comfortable." He was ever of even disposition, kindly, agreeable and congenial.

Death by myocardial infarction came on November 4, 1956. He is survived by his mother, his wife, Margaret Eleanor, and his son, Robert W. Warren.

RALPH F. JACOX, M.D., F.A.C.P.

DR. GEORGE ELLIOTT WOODFORD

It has just been belatedly learned that Dr. George E. Woodford died of an acute coronary thrombosis at his home in Short Hills, N. J., on May 24, 1954. Dr. Woodford was one of the few survivors among the old members of the American Congress on Internal Medicine. He was automatically transferred to Associateship in the College in 1926 when the Congress on Internal Medicine was merged with the College.

Dr. Woodford was born in 1888. He obtained his medical degree in 1913 from the University of Western Ontario Faculty of Medicine. Until the time of his death, he was for many years Medical Director of the Home Life Insurance Company of New York. He had been a member of the Medical Review Panel and Secretary of the Medical Advisory Council, Masonic Foundation for Medical Research and Human Welfare.

Prior to his entrance into the field of insurance medicine, Dr. Woodford had maintained an active practice in Internal Medicine in Detroit, Michigan. His untimely death was deeply mourned by his many friends and colleagues in New York and New Jersey.

He is survived by his widow, Mrs. Erma M. Woodford of Short Hills, N. J., his daughter, Mrs. Roger Adrian Lyon of North Plainfield, N. J., and his sons, George Elliott Woodford, Jr., of Skaneateles, N. Y., and James W. Woodford of Torrance, California.

EDWARD C. KLEIN, JR., M.D., F.A.C.P.,
Governor for New Jersey

DR. I. SIDNEY ZAUR

On July 18, 1956, Dr. I. Sidney Zaur died in Bridgeport, Conn., of hypertension. He was born in Bridgeport, November 1, 1907. He received both his B.S. and M.D. degrees from Yale University, graduating in medicine in 1932. During his college days, he was elected to the honorary Sigma Xi society. He was certified by the National Board of Medical Examiners.

He interned at the Syracuse City Hospital in 1932 and 1933, and at the Bridgeport Hospital in 1934. He then opened his office for the practice of internal medicine in Bridgeport and started an active interest in the Bridgeport Hospital. In 1935, he was appointed Assistant Physician.

His private work consisted of internal medicine and cardiology. He did postgraduate work at the Montefiore Hospital in New York from 1935–1938. He was an Instructor in the Bridgeport Hospital School of Nursing from 1935 until 1948.

Dr. Zaur entered the Medical Corps of the A.U.S. in 1942 as a Captain and spent most of his tour of duty in the South Pacific—going through campaigns of the Solomon Islands, Bismarck Archipelago and the Philippines. He received the Meritorious Service Medal for these campaigns. He was discharged from service in 1946, as Major.

Returning to civilian practice, he was appointed Associate Physician of the Bridgeport Hospital in 1946, and in 1948 he became the hospital Electrocardiologist and Senior Attending Physician. From 1954 to 1956, he was chief of the medical service, after which he became Consulting Physician. In 1952, he was President of the Bridgeport Hospital Medical Staff.

He was certified as a specialist in Cardiology by the American Board of Internal Medicine in 1950. He was also a member of the American Medical Association, the Connecticut State Medical Society, the Fairfield County Medical Society, and Bridgeport Medical Society. He was a Fellow of the American College of Physicians since 1941.

Throughout his career, Dr. Zaur was outstanding in his work, gentle and kind, loved and respected by all his patients, colleagues and friends—he will be greatly missed in Bridgeport.

He is survived by his widow, Mrs. Henrietta Zaur of 15 Stoneleigh Road, Bridgeport 7, Connecticut, and a daughter, Susan, and a son, Allan.

JOHN C. LEONARD, M.D., F.A.C.P.,
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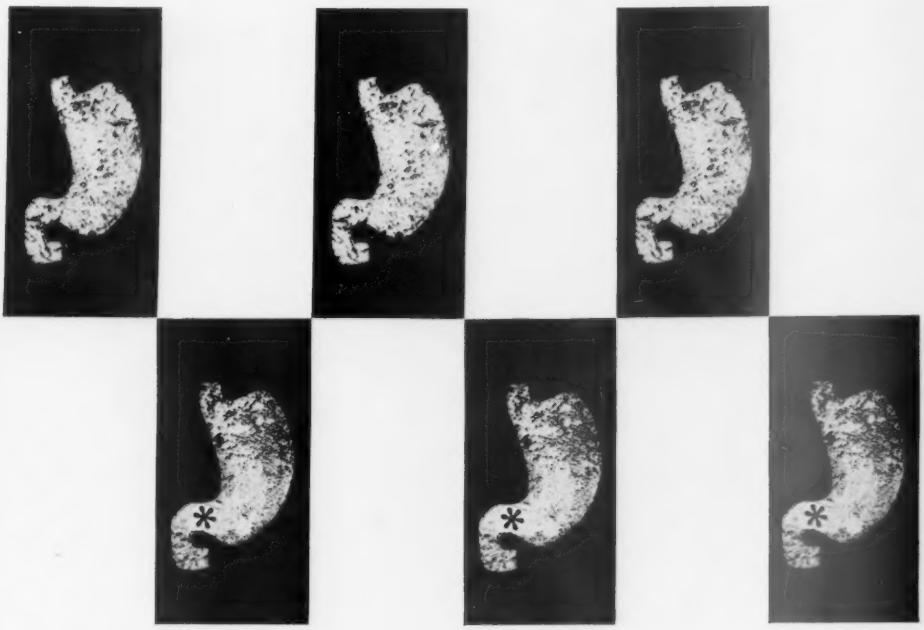

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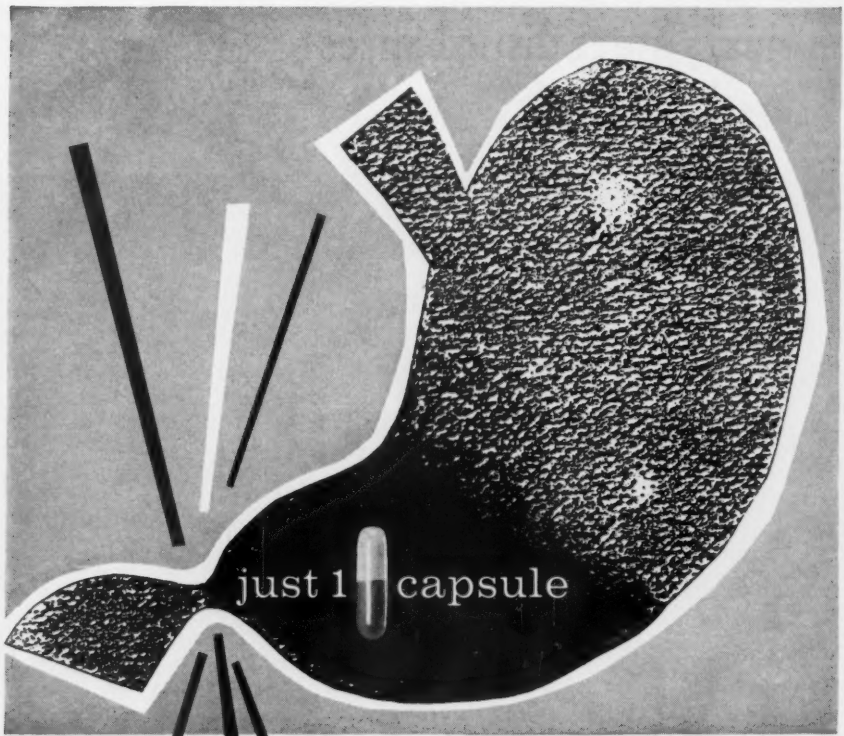

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SQUIBB

1. Glenn, F., Evans, J., Hill, M., and McClenahan, J.: Intravenous cholangiography. Ann. Surg. 140:600 (Oct.) 1954. 2. Sandweiss, D. J., and Fulton, H.: Intravenous cholangiography. J.A.M.A. 159:998 (Nov. 5) 1955.

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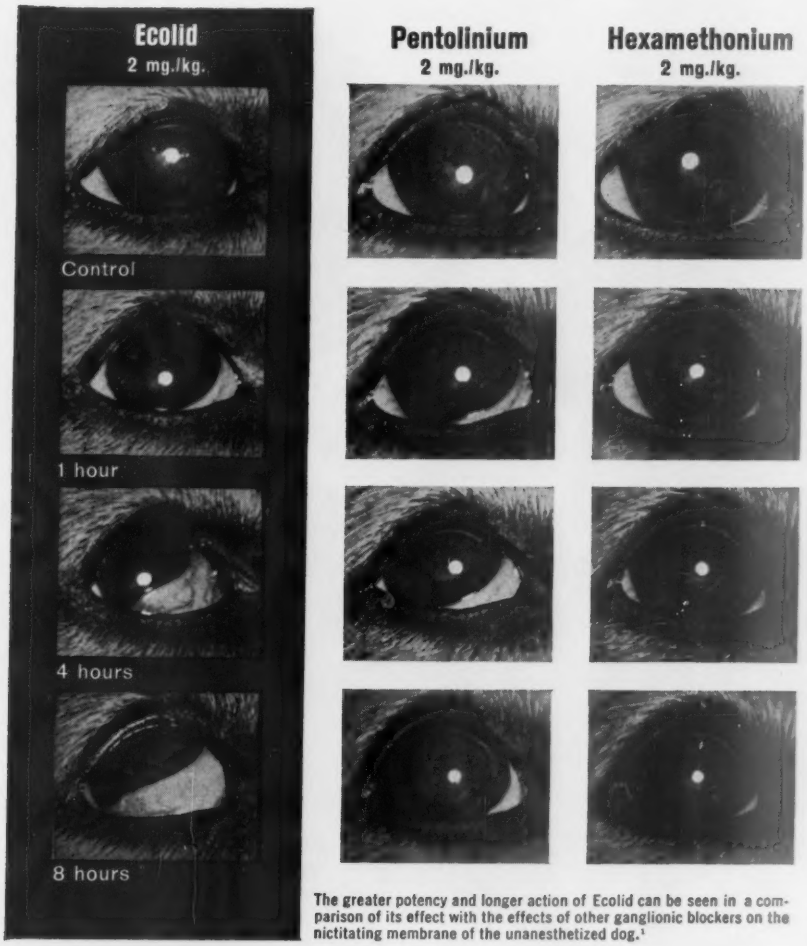

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1. Plummer, A. J., Trapold, J. H., Schneider, J. A., Maxwell, R. A., and Earl, A. E.: J. Pharmacol. & Exper. Therap. *115*:172 (Oct.) 1955. **2.** Grimson, K. S.: J.A.M.A. *158*:359 (June 4) 1955. **3.** Smith, J. R., and Hoobler, S. W.: Univ. Michigan M. Bull. *22*:51 (Feb.) 1956. **4.** Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation *11*:733 (May) 1955.

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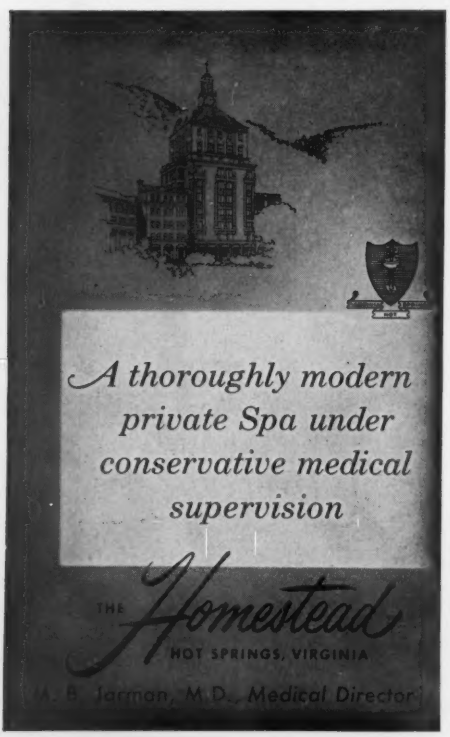
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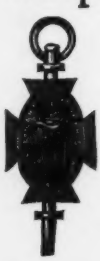

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1. Joint Report of the Technical Group of the Committee on Lipoproteins and Atherosclerosis (Gofman, J.W., et al.) and the Committee on Lipoproteins and Atherosclerosis of the National Advisory Heart Council (Andrus, E.C., et al.): Circulation *14*:691 (Oct.) 1956.
2. Sherber, D.A.: Paper read before the Meeting of the Michigan Academy of General Practice, Detroit, Nov. 7, 1956.

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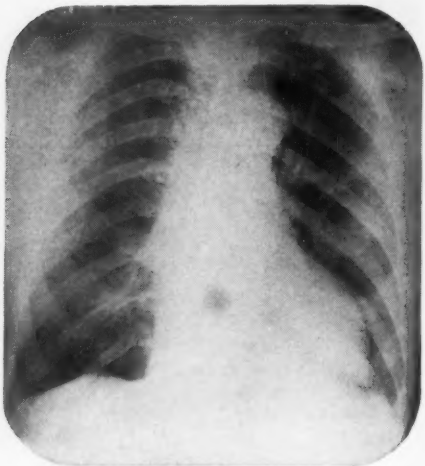

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ARTERIOSCLEROTIC HEART DISEASE

ROENTGEN CONFIGURATION
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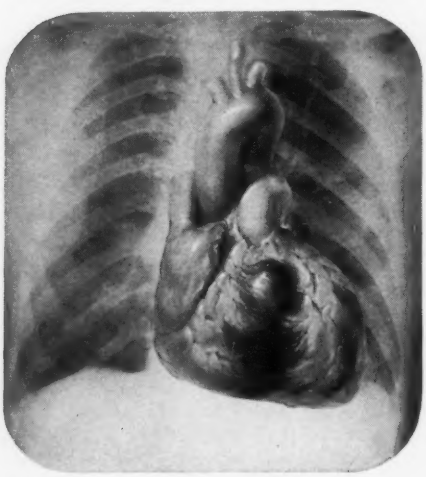

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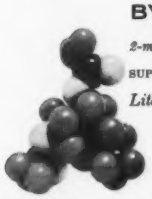

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Thimann, J. and Gauthier, J.W.: Quart. J. Stud. Alcohol. 17: *19, 1956.*

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Borrus, J.C.: J.A.M.A. 157: *1596, 1955.*

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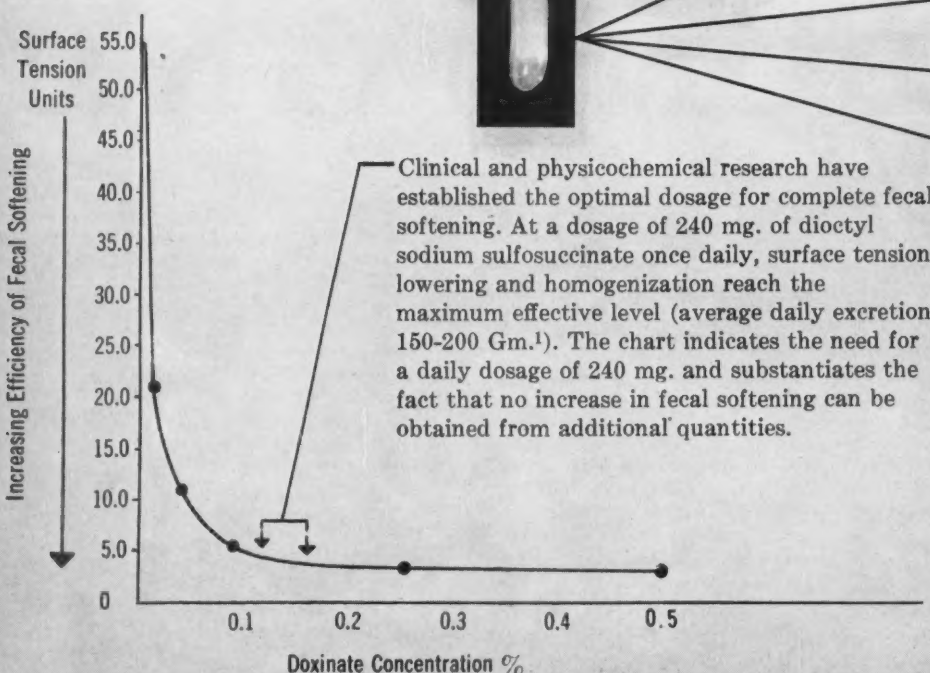

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1. Best & Taylor, The Physiological Basis of Medical Practice, 6th Ed.

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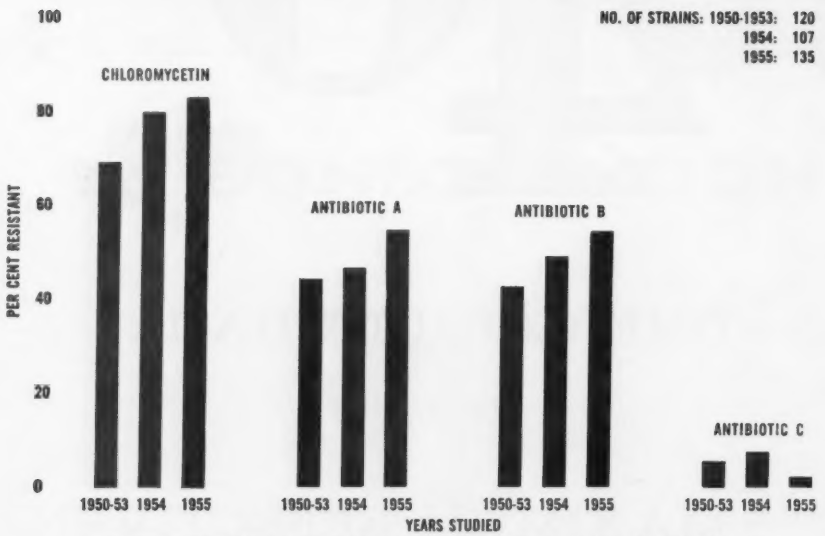

*This graph is adapted from a five-year study by Rantz, L. A., & Rantz, H. H.: *Arch. Int. Med.* 97:694, 1956.

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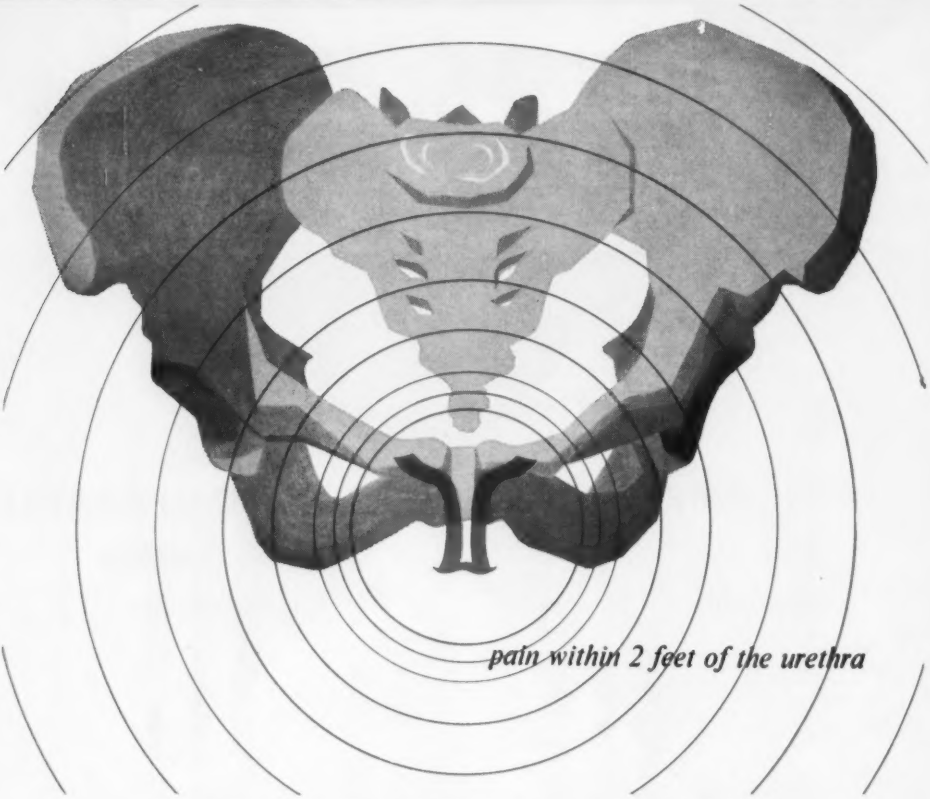

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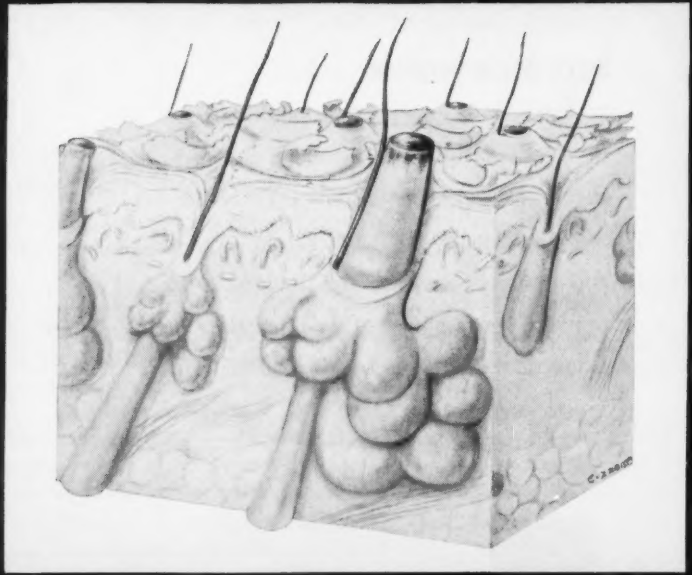

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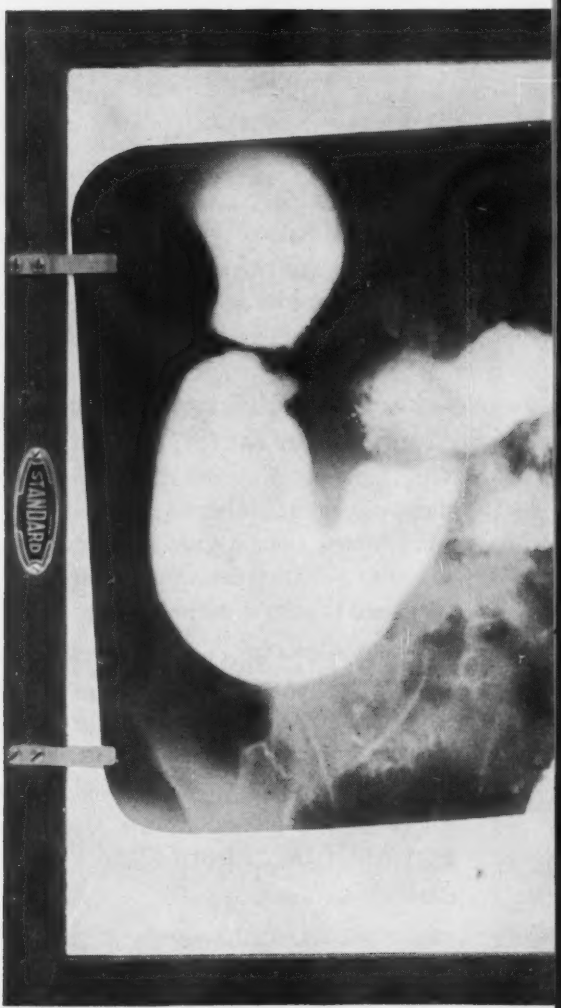

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*U.S. Pat. 2,628,185

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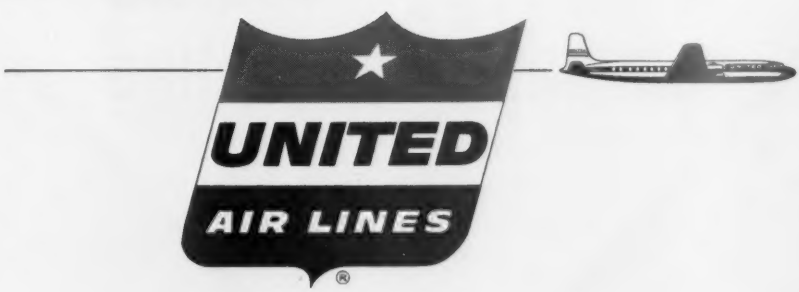

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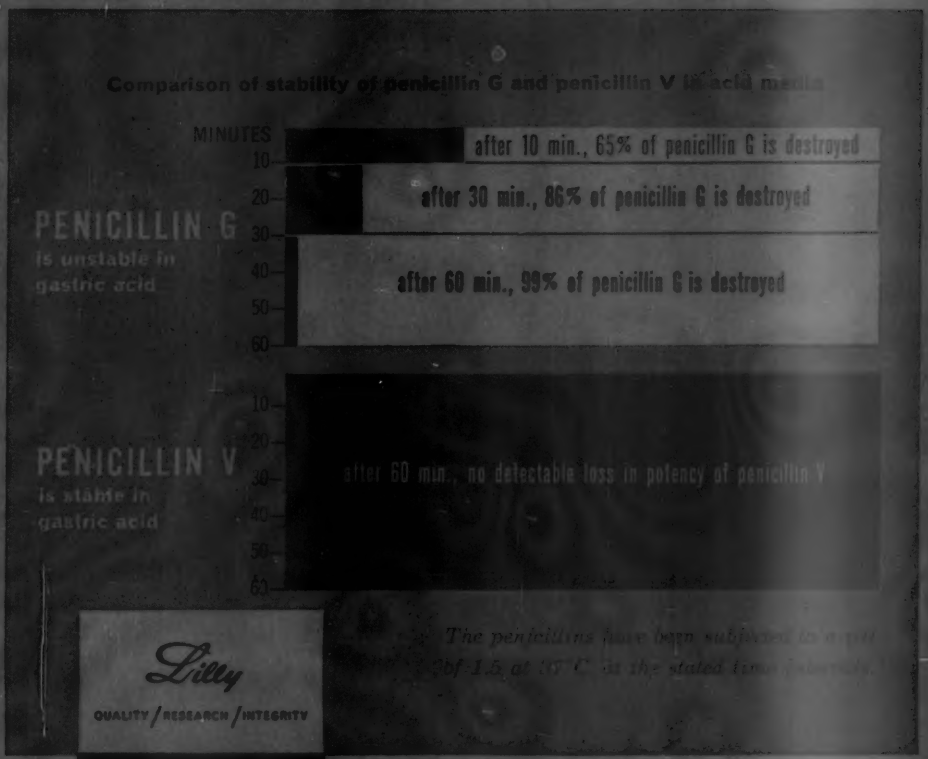
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